CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOME IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME

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Dr TANISH DHIR

DEPARTMENT OF NEPHROLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL
LUDHIANA, PUNJAB-141001

DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled "**CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOME IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME**" submitted towards partial fulfillment of the requirements for the award of **DM NEPHROLOGY** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Preet Mohinder Singh,** Associate Professor, Department of Nephrology, **Dr. Gurdeep Singh Dhooria** Professor, Department of Paediatrics, **Dr. Suman Sethi** Associate Professor, Department of Nephrology. No part of this thesis has formed the basis for the award of any degree previously.

_____

Dr. Tanish Dhir
D.M. Resident
Dept. of Nephrology
DMC & Hospital,
Ludhiana

Date:

Place:

CERTIFICATE OF SUPERVISORS

This is to certify that the work incorporated in this thesis entitled "**CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOME IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME**" has been carried out by **Dr. Tanish Dhir** under our direct supervision. The data incorporated in this thesis is original and genuine and has been carried out by the candidate himself.

Signature of Supervisor

Dr. Preet Mohinder Singh
Associate Professor,
Department of Nephrology
DMCH, Ludhiana

Signature of Co-Supervisors

Dr. Gurdeep Singh Dhooria
Professor,
Department of Paediatrics
DMCH, Ludhiana

Dr. Suman Sethi
Associate Professor,
Department of Nephrology
DMCH, Ludhiana

Date:

ENDORSEMENT BY THE HEAD OF THE INSTITUTE

This is to certify that the thesis entitled "**CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOME IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME**" is a bonafide research work done by **Dr. Tanish Dhir** under the supervision of **Dr. Preet Mohinder Singh,** Associate Professor, Department of Nephrology, **Dr. Gurdeep Singh Dhooria,** Professor, Department of Paediatrics, **Dr. Suman Sethi,** Associate Professor, Department of Nephrology in this institution.

Principal

Dr. Sandeep Puri
Principal
DMC&H, Ludhiana

Date:

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Dr. Tanish Dhir
D.M. Resident
Dept. of Nephrology
DMC & Hospital,
Ludhiana

Date:

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Dedicated

to

my family

&

Teachers

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Dr. Tanish Dhir

ABBREVIATIONS

ACTN4:	Actinin-4
BMI :	Body Mass Index
BP:	Blood Pressure
CDC :	Centers For Disease Control And Prevention
CI :	Confidence Interval
CKD :	Chronic Kidney Disease
CNI :	Calcineurin Inhibitor
CR :	Complete Remission
CsA :	Cyclosporin A
CYC :	Cyclophosphamide
ESKD :	End-Stage Kidney Disease
FSGS :	Focal Segmental Glomerulosclerosis
HDL:	High-Density Lipoprotein
HIV :	Human Immunodeficiency Virus
IL :	Interleukin
INS :	Idiopathic Nephrotic Syndrome
LDL :	Low-Density Lipoprotein
LSRNS :	Late Steroid Resistant Nephrotic Syndrome
MCD :	Minimal Change Disease
MesGN :	Mesangioproliferative Glomerulonephritis
MMF :	Mycophenolate Mofetil
MPGN:	Membranoproliferative Glomerulonephritis
NCEP:	National Cholesterol Education Program
NF-AT :	Nuclear Factor Of Activated T Cells
NOS :	Not Otherwise Specified
NPHS1:	Nephrin
NPHS2 :	Podocin
NR :	Non Response
OPD :	Outpatient Department
ORR :	Overall Remission Rate
PR :	Partial Remission

PRESS :	Posterior Reversible Encephalopathy Syndrome
RCT :	Randomised Control Trial
RR :	Relative Risk
SDNS :	Steroid Dependent Nephrotic Syndrome
SRNS :	Steroid Resistant Nephrotic Syndrome
TAC :	Tacrolimus
Up/Uc :	Urine Protein To Creatinine Ratio
UPCR :	Urine Protein To Creatinine Ratio
URTI:	Upper Respiratory Tract Infection
UTI:	Urinary Tract Infection

ABSTRACT

Introduction: Steroid-resistant nephrotic syndrome (SRNS) accounts for about 10% to 20 % of all nephrotic syndromes in children. The management of SRNS is a herculean task with calcineurin inhibitors being the first line therapy.

Aims and objectives:

- Clinical profile of children with steroid resistant nephrotic syndrome
- Treatment practices and outcomes in these SRNS children

Material and methods: It was an observational study which included SRNS children who were newly diagnosed and those who were known case of SRNS on CNIs and had received 6 months of CNI'S, who presented to the nephrology clinic during Aug, 2021 – May, 2022 period. The clinical profile, histopathological, and biochemical factors and treatment outcomes were recorded and analysed.

Results: 35 children (25 retrospective and 10 prospective) were included. Mean age of onset of Nephrotic Syndrome was 3.82±2.28 years. FSGS was the predominant histopathological lesion. 29 children were given Tacrolimus and 6 were given cyclosporine. After 6 months of CNI's, 88.6% achieved remission and 11.4% children were non responsive (NR). 37.14% children (13/35) had relapse within 1 year. There was statistically significant difference between serum albumin and spot Up/Uc in remission and non remission groups There was also no significant difference in biopsied and not biopsied children based on age of onset of disease, sex, serum albumin, spot UPCR, drug distribution and remission status

Conclusion: We recommend CNI'S as 1st line of therapy for treatment of SRNS and need monitoring of renal function tests to avoid permanent nephrotoxicity. We further recommend starting a CNI in SRNS without waiting for renal biopsy.

Keywords :CNI, UPCR,SRNS.

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INTRODUCTION

Nephrotic syndrome is the most common glomerular disease in the childhood. It usually begins between the age of 2 - 5 years. Diagnosis of nephrotic syndrome requires the presence of Nephrotic range proteinuria: >=3 + by dipstick or proteinuria >40mg/m2 /hr (>1000mg/m2 /day) or urine protein to creatinine ratio (Up/Uc)>=2mg/mg, hypoalbuminemia (< 3g/dl) or edema.[1] Idiopathic nephrotic syndrome (INS) represents more than 90% of cases between 1 - 10 years of age and 50 % beyond 10 years of age. [2]

The prevalence of Idiopathic Nephrotic syndrome varies from 12-16 per 100000 children.[3] Majority of children have Minimal Change disease (MCD) with more than 90% of children responding to long term steroid therapy while only 50% of mesangial proliferation and 30% of focal segmental glomerulosclerosis responds to steroid therapy. [4]

Majority of the children achieve remission after starting prednisolone at a dose of 2mg/kg/day (60mg/m2/day) or 120mg/m2 every other day in 2 or 3 divided doses in 4 weeks. 10-20% children have no response to steroid and are considered as Steroid Resistant Nephrotic syndrome (SRNS) while there are some children that relapse after lowering the dose or stopping the steroid and are considered as Steroid Dependent Nephrotic Syndrome (SDNS).

SRNS is defined as absence of complete remission of proteinuria despite 4 weeks of therapy with full dose prednisone (2 mg/kg/day or 60mg/m2 /day) either at disease onset (initial, primary) or following a subsequent relapse (late, secondary).

There is variability in the prevalence of SRNS depending on the ethnicity with a prevalence of about 20% among European children to 27% to 54% among Asians. [5, 6]

History and examination might help identify genetic and secondary forms of SRNS. History of deafness, developmental delay, seizures, family history of similar disorder and consanguinity, and syndromic features or extrarenal anomaly (e.g., genitourinary abnormality, microcoria, dystrophic nails and microcephaly) suggest a genetic etiology. History of joint pain, weight loss, alopecia, jaundice, rash, or palpable purpura indicates a secondary cause.

Screening for viral infections: Patients should be evaluated for hepatitis B and C, and HIV infections. Collapsing FSGS (Focal Segmental Glomerulosclerosis) may be associated with HIV or parvovirus infection.[7] Those with positive serology are evaluated for viral load and extent of disease. Active infection may require the use of antiviral therapy

Patients with steroid-resistant disease pose the most difficult therapeutic challenge. These children are at risk for complications of unremitting nephrotic syndrome and developing end-stage kidney disease (ESKD) in the long term. Medications like cyclosporine, tacrolimus, intravenous steroids, and most recently rituximab are used for inducing and maintaining remission in these patients; these drugs cause intense immunosuppression.

The management of steroid resistant nephrotic syndrome, which accounts for 10%–15% of nephrotic syndrome in children, is a herculean task. [8] All SRNS patients should undergo a kidney biopsy to determine the histopathological pattern.

Biopsies are examined by light, immunofluorescence, and electron microscopy. An adequate biopsy should include the corticomedullary junction and have ~ 20 glomeruli to identify focal pathology like FSGS. [9] A biopsy is useful for: (i) identifying pathology, extent of interstitial fibrosis and glomerulosclerosis for diagnosis and prognosis;

and (ii) excluding differential diagnosis and secondary causes of nephrotic syndrome. Repeat biopsy is required to assess calcineurin inhibitor (CNI) toxicity, progression of disease or change in pathology

Renal histology shows Focal segmental glomerulosclerosis (FSGS), Minimal change disease (MCD), Mesangioproliferative Glomerulonephritis (MesGN). Other patterns, including C3 Glomerulopathy, Membranous Nephropathy and IgA nephropathy, and secondary causes of nephrotic syndrome are uncommon. Histology suggestive of FSGS is considered a risk factor for progression to CKD (chronic kidney disease). [10, 11, 12, 13] A kidney biopsy is not necessary in patients with well described monogenic form of SRNS, known to be unresponsive to immunosuppression, e.g., congenital nephrotic syndrome, familial disease, or if a known genetic cause is already identified.

The management of these SRNS patients are challenging with unsatisfactory quality of life, morbidity due to infectious and non-infectious illnesses and side effects of intensified immunosuppression. [8, 14] With the difference in pathogenesis, treatment response, and outcomes, individualization of the cause and subsequent therapy is needed.

Immunosuppressant drugs such as Cyclosporine-A have been used in patients who have no response to steroid but the treatment options like Cyclosporine-A have high relapse and resistant rate. [15] Othertreatment options include CNI's like tacrolimus which can be used and have a documented better safety profile with a higher remission and a lower relapse rate.[16] Tacrolimus and prednisolone are effective, safe, and preferable to cyclophosphamide as the initial therapy for patients with steroid resistant nephrotic syndrome. [17, 18] Tacrolimus is preferred to cyclosporine except in children who are unable to swallow tablets (cyclosporine is available as suspension), and patients with

seizures or at risk for diabetes. Doses of tacrolimus and cyclosporine are titrated to achieve recommended trough levels, keeping in mind interaction with other medications. Low levels are associated with non-response and relapse, while high levels increase the risk for nephrotoxicity. [19] Lower levels may be targeted once sustained remission is achieved for 6-9 months. [20, 21] Most patients who respond to CNI do so within the first 6-months of treatment. [17, 22, 23, 24] Non-response to CNI is therefore considered in patients who continue to show nephrotic-range proteinuria, hypoalbuminemia, or edema despite 6-months therapy. Patients showing non-response should be screened for significant genetic variations, and considered for alternate management. Stoppage of steroid therapy might not be possible in patients with multiple relapses. It is documented that Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid resistant nephrotic syndrome. [25]

In patients with non-genetic form of SRNS (25-35%) who do not show complete or partial remission and are non-responsive to therapy with CNI, Rituximab has been tried but its efficacy is less satisfactory with complete or partial remission observed in 46.4% with better response in MCD (63.2%) than in FSGS (39.2%) and late (52.8%) compared to initial resistance (40.8%).[26]

Children with SRNS are at risk for progression to stage 5 CKD, complications of the disease and adverse effects of medications. [27, 28, 29] Managing immunosuppressive therapies is a challenge due to the risk of infections, noncompliance, and presence of co-morbidities. Patients require regular monitoring and careful follow up, and counseling regarding need for compliance with medications.

Thereby NS is a chronic condition with the treatment of SRNS being a difficult task. [17] The most important predictor of long-term outcome is complete or partial remission of proteinuria with patients with

persistent proteinuria at risk for progressive renal failure. [30] The response of proteinuria to therapy is an essential determinant of Renal survival [31] as determined by the Data from PodoNet Registryon patients with SRNS which shows that 10-year survival was highest (94%) in complete remission, 72% with partial remission and 43% with non-response. [32] While the information on long-term outcomes of SRNS is available for Caucasian and African American children, studies from India have looked mostly at the short-term outcomes after the administration of different immunosuppressive agents. [33, 34] Ethnicity appears to influence the outcomes, and as most children with SRNS receive calcineurin inhibitors (CNI's), the long-term outcome is also dependent on the response to these agents and their inherent nephrotoxicity. [33, 35] There are no studies on clinical profile and management options in SRNS in our region. Hence, need of this study is required.

AIMS AND OBJECTIVES

1. Clinical profile of children with Steroid Resistant Nephrotic Syndrome (SRNS)

2. Treatment practices and outcomes in these SRNS children

REVIEW OF LITERATURE

The clinical profile, treatment practices are important factors associated with remission of SRNS children. Various immunosuppressants have been studied to induce and maintain remission. CNI's are usually the first line therapy. These drugs are associated with side effects and these children are at high risk to progress onto chronic kidney disease.

The immunosuppressants cyclosporin A (CsA) and Tacrolimus (TAC) suppress the immune response by inhibiting signal transduction pathways. CsA and Tacrolimus bind to their intracellular receptors, immunophilins, thereby blocking activity of specific targets like Calcineurin. Due to the large surface area of interaction of the drug–immunophilin complex with calcineurin, the specificity of Tacrolimus and CsA for their biologic targets is comparable to growth factor– receptor interactions. Thereby, all the benefits as well as side effects of these drugs are due to inhibition of calcineurin. Inhibition of the action of calcineurin blocks the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT), resulting in a failure to activate the genes regulated by the NF-AT transcription factor. These genes include those required for B-cell such as interleukin (IL-4) and CD40 ligand as well as those necessary for T-cell proliferation such as IL-2. [18]

Various studies have been done to evaluate the outcomes in SRNS children.

Use of Tacrolimus was studied in a RCT (Randomized Control Trial) conducted by Choudhary et al in a tertiary-care hospital with 41 consecutive patients with idiopathic SRNS, estimated glomerular filtration rate greater than 60 mL/min/1.73 m2, and histological characteristics showing minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis. In this

study children were randomly assigned to treatment with tacrolimus (n= 21) or CsA (n = 20). Tacrolimus (0.1 to 0.2 mg/kg/d) or CsA (5 to 6 mg/kg/d) was given for 1 year, cotreatment with alternate-day prednisolone and enalapril was done. After 6 months of therapy, remission occurred in 18 (85.7%) and 16 patients (80%) treated with tacrolimus and CsA, respectively (relative risk [RR], 1.07; 95% confidence interval [CI], 0.81 to 1.41). Rates of remission at 12 months were also similar (RR, 1.14; 95% CI, 0.84 to 1.55). The proportion of patients who experienced relapse was significantly greater in those receiving CsA compared with tacrolimus (RR, 4.5; 95% CI, 1.1 to 18.2; P = 0.01).Tacrolimus or CsA in combination with low-dose steroids show similar efficacy in inducing remission in patients with SRNS. Therapy with tacrolimus is a promising alternative to CsA in view of the lower risk of relapses and lack of cosmetic side effects. [17]

Another study by Becknell B et al. suggested tacrolimus to have better results in steroid resistant cases. The study was the first prospective, randomized, multicenter trial of intravenous cyclophosphamide versus tacrolimus in 131 children with SRNS. Consecutive patients aged 2–16 years with biopsy-confirmed minimal-change NS (MCNS), FSGS, or mesangioproliferative glomerulonephritis were stratified by early and late steroid resistance and randomized to 12 months of tacrolimus or 6 monthly infusions of cyclophosphamide. Each group received alternate-day prednisolone. The primary end point was the proportionof patients with complete or partial remission, on the basis of first- morning urine protein-to-creatinine ratios at 6 months. Complete or partial remission rates were higher in patients receiving tacrolimus (82.5%) versus cyclophosphamide (45.9%), and sustained remission or steroid-sensitive disease was higher in the tacrolimus group at 12 months (52.4% versus 14.8%). They concluded that prescription of tacrolimus and prednisolone is effective, safe, and superior to

intravenous cyclophosphamide as the initial therapy for children with SRNS. [23]

Loeffler et al reported the use of tacrolimus in seven children with SRNS; six children achieved CR and one went into PR after a mean duration of 2 months of therapy. Five of the seven children were off steroids on follow-up, although the steroid-free duration was quite short.[36]

Children with steroid-resistant nephrotic syndrome (SRNS) are at risk of developing renal failure. A study by Butani L et al showed results of a single-center retrospective observational study of the remission rate in pediatric patients with SRNS receiving tacrolimus. Serial renal biopsies from children on tacrolimus therapy were evaluated for tubulointerstitial fibrosis and transforming growth factor-beta immunostaining. Of the 16 children with SRNS, 15 (93.75%) went into complete remission after a median of 4 months of therapy. Nine children were able to stop steroids, while the others were on tapering doses. Forty-seven percent had relapses, most of which were steroid-responsive. Serial renal biopsies were obtained from seven children after median treatment duration of 24 months; two of these children had increased tubulointerstitial fibrosis and four showed increased transforming growth factor-beta tissue staining. Children with worsening histological findings were younger. There was no significant association between tacrolimus exposure and biopsy changes, although the average trough level was higher in those children with worsening histological findings. They thereby concluded that, tacrolimus may be a safe and effective alternative agent for inducing remission in children with SRNS. [37]

A retrospective chart review was performed by Straatmann C et al on patients diagnosed with idiopathic NS and subsequent LSR (Late Steroid Resistance) during the 8-year study period from 2002 up to and including 2009, with a minimum of 2 years of follow-up. Primary outcome measures were proteinuria and renal function. A total of 29 patients were classified as having LSRNS (Late Steroid Resistant Nephrotic Syndrome). The majority of patients received treatment with

calcineurin inhibitors and/or mycophenolate mofetil. Seven patients received three or more non-steroid immunosuppressant medications. Sustained complete or partial remission was achieved in 69 % of patients. Three developed end stage renal disease, and all others maintained normal renal function. There were 13 episodes of serious adverse events, none of which were fatal or irreversible. Thereby most patients with LSRNS responded to immunosuppressive therapy by reduction or resolution of proteinuria and preservation of renal function. The results suggest that immunosuppressive treatment is a viable option in NS patient who develop LSR. [38]

Another study was done at AIIMS Delhi by Sinha A et al by following six months of therapy with tacrolimus, patients with complete or partial remission were randomly assigned such that 29 received MMF while 31 received tacrolimus along with tapering prednisolone on alternate days for 12 months. The proportion of patients with a favorable outcome (sustained remission, infrequent relapses) at one year was significantly lower (44.8%) in the MMF group than in the tacrolimus group (90.3%). The incidence of relapses was significantly higher for patients treated with MMF than tacrolimus (mean difference: 1.05 relapses per person-year). While there was no difference in the proportion of patients with sustained remission, the risk of recurrence of steroid resistance was significantly higher for patients receiving MMF compared to tacrolimus (mean difference: 20.7%). Compared to tacrolimus, patients receiving MMF had a significantly (71%) lower likelihood of a favorable outcome and significantly increased risk of treatment failure (frequent relapses, steroid resistance). Thus, replacing tacrolimus with MMF after six months of tacrolimus therapy for steroid-resistant nephrotic syndrome in children is associated with significant risk of frequent relapses or recurrence of resistance concluding tacrolimus to be superior to mycophenolate mofetil in sustaining remission in children with idiopathic steroid resistant nephrotic syndrome. [25]

Supavekin S et al did a retrospective chart review of 18 children who received prednisolone at the start of tacrolimus. 72.2% children achieved complete response (CR), medicine was well tolerated and treatment was effective. [39]

In a prospective non-randomized, non-controlled study by chen, HX et al Chinese children with SRNS who failed the previous full-dose prednisone treatment were given tacrolimus (0.1 mg/kg/day) and low-dose prednisone (0.25–0.50 mg/kg/day) and compared the overall remission rate (ORR) and adverse events in the follow-up period with this therapeutic regimen. A total of 76 children were enrolled into the study with an average follow-up period of 18 ± 6 months (maximum 36 months). ORR achieved by the first, third, and sixth months was 94.7%, 94.7%, and 96.0%, respectively. All patients who attained an initial tacrolimus trough concentration > 6 ng/ml (60.3%) achieved remission. The relative risk of relapse at < 3 ng/ml compared to 3–6 ng/ml, 6–9 ng/ml, and 9–12 ng/ml was 2.3, 3.2,and 16.9, respectively. During the follow-up period, adverse effects thathad been previously reported were rare. [40]

In a prospective study by Prasad N et al, Forty-five children with SRNS who were also resistant to Cyclophosphamide (CYC) (CYC- SRNS) from January 2006 to June 2011, were included in the study. Patients were treated with CNI either TAC or CSA based on 1:1 allocation and were prospectively observed. Patients who were nonresponsive to CNIs had been treated with mycophenolate mofetil. Outcomes were measured in terms of remission of NS, adverse effects of drugs, and progression of disease. After 6 months of treatment, 16/23 (69.5%) patients on CSA achieved remission and 18/22 (81.8%) on TAC achieved remission ($P = 0.3$). The side effects hypertrichosis, and gum hyperplasia were significantly less in TAC group as compared to CSA group ($P < 0.001$). The 1-, 2-, 3-, 4-, and 5-year estimated renal survival (doubling of serum creatinine as event) in CSA group was

96%, 91%, 85%, 54%, and 33% and in TAC group was 96%, 95%,90%, 89%, and 79%, respectively (P = 0.02). Although TAC and CSA are equally efficacious, TAC has significantly less side effects. The long-term outcome of renal function was significantly better in patients who were treated with TAC as compared to CSA. [33]

In a study by Klaassen et al Thirty-six patients with SRNS were studied retrospectively. Median age at presentation was 3.2 (range, 0.06–15.0) and median follow-up 15.5 years (range, 1.8–27.7), respectively; 23 (64 %) had focal segmental glomerulosclerosis (FSGS) on biopsy. In 33/36 patients (92 %), genetic testing was performed for at least three most common genes known to be mutated in SRNS. Nineteen patients (53 %), especially those with minimal change nephrotic syndrome (MCNS) at initial biopsy ($p < 0.002$), entered complete remission with CSA monotherapy, including one patient with compound heterozygous *NPHS1* and dominant *ACTN4* mutation, respectively. Ten patients entered partial remission (28 %, all FSGS), including two with *NPHS2* mutations. Seven patients (six FSGS, one MCNS) did not respond to treatment. In 15 of 19 responders to CSA, treatment was stopped after a median of 3.1 years (range, 0.5–14) and no further relapses occurred in 11/15 (73 %) patients with median follow-up of 9.7 years. CSA monotherapy is effective in SRNS. Discontinuation of CSA is possible in many patients with complete remission. [41]

A study conducted by Sanjeev Gulati et al to evaluate the safety and efficacy of tacrolimus (TAC) in children with SRNS was done. The study group comprised of 22 consecutive children with steroid-resistant nephrotic syndrome (SRNS) who were studied prospectively. TAC was initiated with a dose of 0.10 mg/kg/day, and the dose was increased to attain a trough level of 5.0-10.0 g/l. These patients were treated with concomitant prednisone, which was subsequently tapered off and stopped. The primary outcome variable was the number of

patients who attained a complete remission (CR) or partial remission (PR). The mean age of onset was 7.33 +/- 5.9 years, and there were 20 boys and 2 girls. Of the 22 children, 9 had minimal change disease, 11 had focal segmental glomerulosclerosis and the other 2 had diffuse mesangial hypercellularity on histopathology. TAC had to be withdrawn in 3 children because of its side effects. Of the remaining 19 children who received adequate therapy and were able to achieve target levels, CR was seen in 16 (84%) children, 2 (10.5%) attained PR and 1 was nonresponsive. The mean time to achieve remission was 63.2 +/- 44 days and the mean dose of TAC was 0.18 +/- 0.07 mg/kg. The mean urine spot protein/creatinine ratios were significantly lower (0.33 +/-0.58 vs. 13.5 +/- 21.9 mg/mg, p = 0.002) and the mean serum albumin levels were significantly higher (3.92 +/- 0.35 g/dl vs. 2.39 +/- 0.56 g/dl, p = 0.00005), as compared to those prior to starting TAC. The mean glomerular filtration rate values at the end of the study were similar to those prior to starting TAC (97.9 +/- 21.2 ml/min/1.73 m(2) vs. 96.4 +/-18.4 ml/min/1.73 m (2), p = 0.30). The mean duration of follow-up was 290 +/- 126 days. The results suggest that TAC is an effective therapeutic modality for SRNS, including the subgroup of children who are nonresponsive to the current therapeutic modalities like cyclophosphamide and cyclosporine. [42]

In a study conducted by Agrwal S et al,Ninety-one (72 boys) children with a median (interquartile range [IQR]) age of onset of nephrotic syndrome as 48 (24–87) months were included. MCD and FSGS were the most common histopathological types (57.1% and 36.3%, respectively) and 62 (68.1%) patients had late steroid resistance. Calcineurin inhibitors (CNIs) were used in 86.8% of the children, and response rates with cyclosporine and tacrolimus for complete remission (CR) were 80% and 73.7%, respectively, with median (IQR) time to response being 3 (2–4) months. The presence of MCD on histology and the use of CNIs were significantly associated with CR ($P < 0.01$). At a median (IQR) follow-up of 5 (3–7) years, 76 (83.5%) children had either CR or partial remission, four (4.4%)

developed chronic kidney disease and five (5.5%) died (three due to end-stage renal disease and two of infective complications). The study concluded that SRNS children with MCD on biopsy, late resistance, and response to CNIs have better long-term outcomes. Most patients respond to CNIs within the first 6 months of use and need therapy for at least 24 to 36 months. [43]

Statuses of patients are defined according to the following categories:

Remission- Urine albumin nil or trace for 3 consecutive early morning specimens,

Relapse- Urine albumin 3+ or 4+ for 3 consecutive early morning specimens, Up/Uc>2, or 24-hrprotein >1000 mg/m2 /day, in a patient previously in partial or complete remission

Sustained remission- No relapse for 1 year

Frequent Relapsers - Two or more relapses in initial six months or more than three relapses in any twelve months.

Infrequent Relapsers - Patients who have three or less relapses a year

Steroid resistance - Absence of remission despite therapy with daily prednisolone at a dose of2 mg/kg per day for 4 weeks.

MATERIAL AND METHODS

Design – Observational study.

Setting – Nephrology and Paediatric Nephrology clinic of a tertiary care hospital, DMCH Ludhiana

Source of Data - Source of data was patients between 3 months to 18 years of age who were:

1. Newly diagnosed SRNS cases
2. Follow up of those patients who were already known case of SRNS and were on immunosuppressants for at least 6 months.

Inclusion criteria

1. All newly diagnosed SRNS patients (Nephrotic syndrome children >=3+ Dipstick or proteinuria >40mg/m2 /hr (>1000mg/m2/day) or Up/Ucr >=2mg/mg, Hypoalbuminaemia (<3gm/dl) or edema) who have received 4 weeks of full dose steroids (2mg/kg/day) and there is absence of complete remission.

2. All SRNS patients who were already on Immunosuppressants with follow up of at least 6 months.

Exclusion criteria

- Patients of congenital Nephrotic syndrome (age at onset <3months)
- Patients with nephrotic syndrome due to secondary causes.
- Steroid Sensitive Nephrotic Syndrome

- If attendants refused to give consent for participation in the study.

Consent

Written consent was obtained from the attendants of the children. Patients were assessed appropriately and data was collected on specified patient proforma including information such as age, sex, Steroid Resistant Early/Late, Age of onset, weight, height, BMI, side effects.

CLASSIFICATION OF RESPONSE

1) Responder = Patient who achieved Complete remission/ Partial remission at 6 months of treatment.
2) Non-Responder = Patient showing no response to treatment.

Complete Remission is defined as the Urine albumin nil or trace for 3 consecutive early morning specimens, Up/Uc < 0.2 gm/dl; and absence of edema;

Partial Remission is defined as 1+/2+ (dipstick), Up /Uc 0.2-2, or 24-hr protein 100-1000mg/m2/day; serum albumin >=3gm/dl; and absence of edema;

Nonresponse is defined as 3+/4+(dipstick), Up/Uc >2 or 24-hr urine protein >1000mg/m2 /day; Albumin < 3 g/dL or edema

Treatment Failure, defined in patients showing no response despite 6 months of treatment, persistent nephrotoxicity, or death.

Treatment Protocol

Children with SRNS were treated with immunosuppressants. They were either given Cyclosporine or Tacrolimus with tapering dosage of prednisolone. Cyclosporine was given at a dose of 4-5mg/kg/day as two divided doses and Tacrolimus was given in doses ranging 0.07-0.15mg/kg/day as two divided doses. They were followed up with regular monitoring of Serum albumin, Proteinuria measured as Spot UPCR, renal function tests, any side effects at regular intervals. Serum levels of CNI was not done in all patients due to financial constraints.

Method of Collection of Data

It was an observational hospital-based study of patients from August, 2021 to May, 2022 of SRNS who were newly diagnosed along with patients who were already known case of SRNS and were on immunosuppression with follow up of at least 6 months.

Outcome

Primary outcome -The primary end point was the proportion of patients achieving complete or partial remission at the end of 6 months of therapy.

Secondary outcome - Included frequency of relapses, renal dysfunction and side effects from immunosuppressive medications.

Statistical Analysis

Analysis was done by SPSS 21.0 (Statistical Product and Service Solutions Chicago 21.0 version). Continuous data was presented as mean, 95% confidence interval (CI), and range unless other- wise stated.

OBSERVATIONS AND RESULTS

We conducted a retrospective and prospective study of SRNS children attending OPD in Nephrology clinic of Dayanand Medical College and Hospital, Ludhiana during study period from Aug, 2021 to May, 2022.

Table No. 1: Distribution of Study Participants

Case Distribution	No. of cases	Percentage
Retrospective	25	71.4%
Prospective	10	28.6%
Total	35	100.0%

Out of 35 children enrolled in the study, 25 were retrospective cases accounting for 71.4% of the cases and 10 were prospective cases accounting for 28.6% of the cases.

Table No. 2: Distribution of Study Participants Based On Type of Immunosuppression Given

Treatment regimen	No. of cases	Percentage
Cyclosporine	6	17.1%
Tacrolimus	29	82.9%
Total	35	100.0%

Out of 35 children enrolled in the study,29 children were given Tacrolimus and 6 children were given cyclosporine

1. Demographic Data

A) Age

1) Age Of Onset Of Nephrotic Syndrome

Table No. 3: Age of Onset of Nephrotic Syndrome

Age Of Onset (Yrs.)	Frequency	Percent
< 2	5	14.2%
2-8.0	28	80%
> 8	2	5.7%
Total	35	100%

In our study group of 35 children, most common age group of onset of Nephrotic Syndrome was between 2-8 years (80%), followed by <2 years (14.2%), followed by > 8 years (5.7%).

2) **Mean Age of Onset Of Nephrotic Syndrome**

Table No. 4: Mean Age of Onset of Nephrotic Syndrome

Age of Onset	N	Mean	Std Deviation	Minimum	Maximum
	35	3.82	2.28	0.90	12.00

Mean age of Onset of Nephrotic Syndrome was 3.82±2.28 years, minimum age being 9 months and maximum being 12 years.

3) **Age Groups**:

Table No: 5: Distribution of Study Participants Based On Age Group at Time of Enrolment

Age groups	No. of cases	Percentage
1-5 YRS	9	25.7%
6-12 YRS	22	62.9%
13-18 YRS	4	11.4%
Total	35	100.0%

In our study group, we observed 9 children in the age group of 1-5yrs accounting for 25.7% cases, 22 in the age group 6-12yrs accounting

for 62.9% of cases and 4 in the age group 13-18yrs accounting for 11.4% of the cases at the time of enrolment

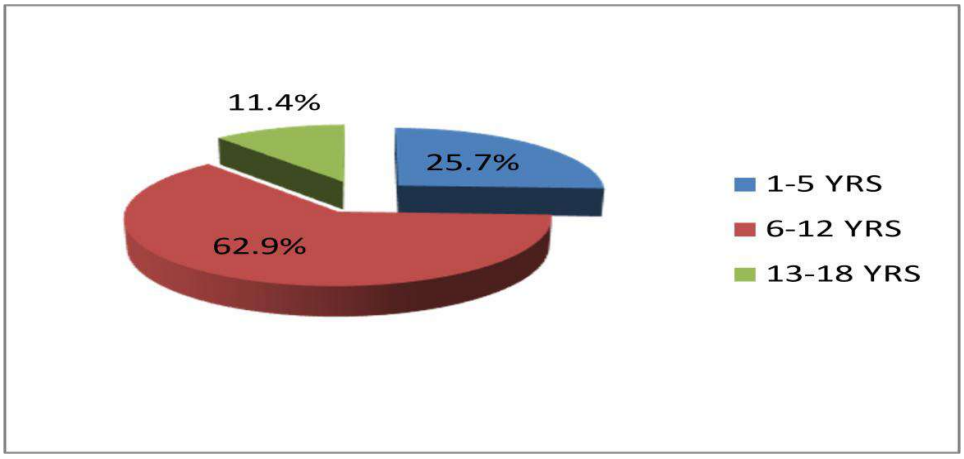

Figure 1: Distribution of Study Participants Based On Age Group at Time of Enrolment

B) Sex

Table No. 6: Distribution of Study Participants Based On Gender

Sex	No. of cases	Percentage
F	10	28.6%
M	25	71.4%
Total	35	100.0%

In our study group, there were 25 male children and 10 female children showing male predominance.

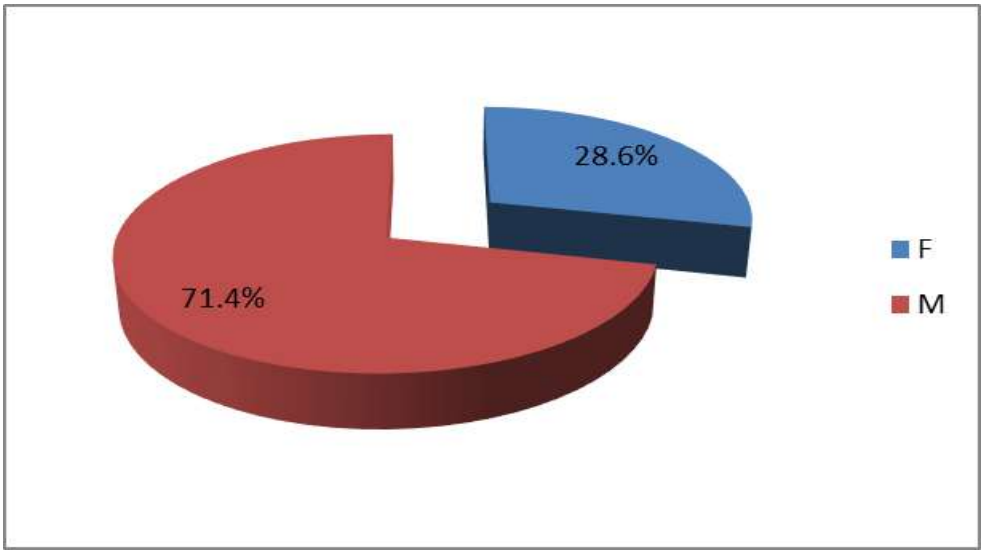

FIGURE NO 2: STUDY PARTICIPANTS BASED ON GENDER

C) Body Mass Index

Table No. 7: Distribution Of Study Participants Based On BMI

BMI	Number	Percentage%
Underweight (< 5th percentile)	3	8.5%
Normal (5th- 85th percentile)	22	62.8%
Overweight (85th-95th percentile)	1	2.8%
Obese (>95th percentile)	9	25.71%
Total	35	100%

In our study group of 35 Children, 22 out of 35 children (62.8%) were having normal BMI, 9 were Obese (25.71%), 3 were underweight (8.5%) and 1 was overweight (2.8%); defined as per CDC guidelines.

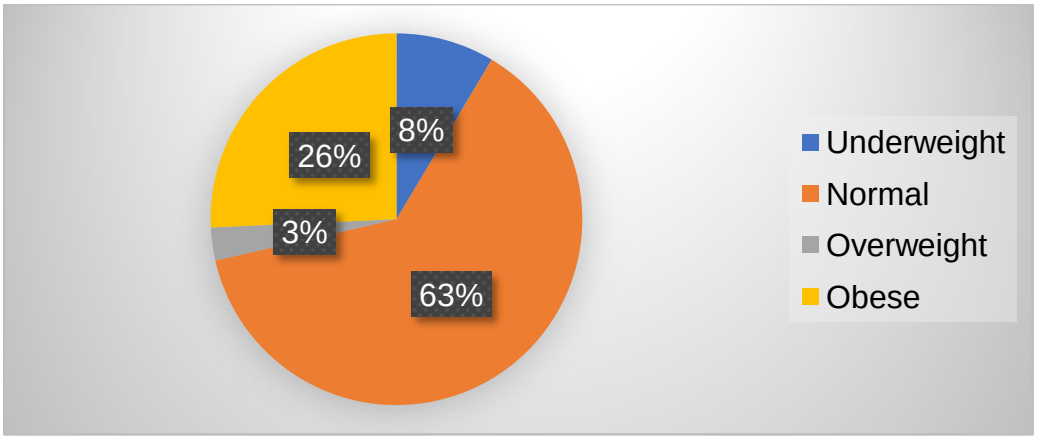

Figure No. 3 Distribution Study of Participants Based On BMI

D) Regional Distribution

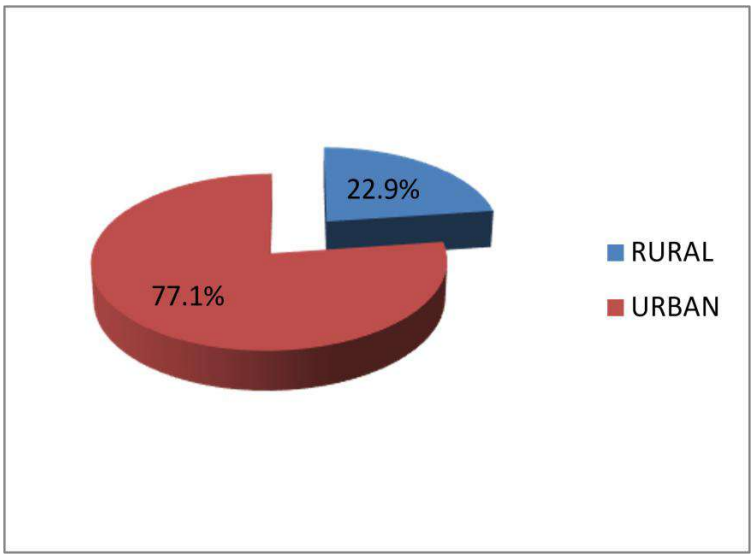

Figure No. 4: Regional Distribution of Study Participants

In our study group there were 27 urban and 8 rural children showing Urban Predominance.

2. Associated Findings:

A) Hypertension

Out of 35 children, 4 Children presented with Hypertension at Onset with BP readings above 95th percentile of that age group making it 11.4 %.

B) Microscopic Haematuria

Out of 35 children, 2 children presented with microscopic haematuria accounting for 5.7% of all the cases.

C) Dyslipidaemia

Table No. 8: Distribution of Study Participants as Per Associated Findings

	No. of cases	Percentage
1.Hypertension at onset	4	11.4%
2.Microscopic Haematuria at onset	2	5.7%
3. Dyslipidaemia		
A) ↑Cholesterol	29	82.86%
B) ↑ Triglycerides	34	97.14%
C) ↑LDL	3	8.57%
D) ↓ HDL	20	57.14%

Out of 35 children, Cholesterol levels were increased in 29 children, LDL in 3, Triglycerides in 34 & HDL was decreased in 20 children as per NCEP Expert Panel on cholesterol levels in children.

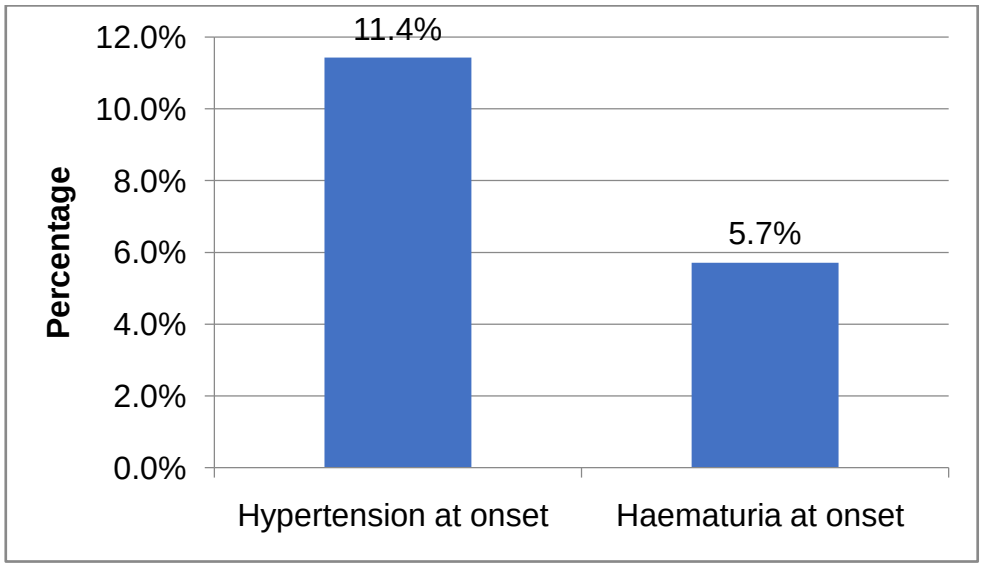

FIGURE NO 5: Associated Findings In Chidren With SRNS

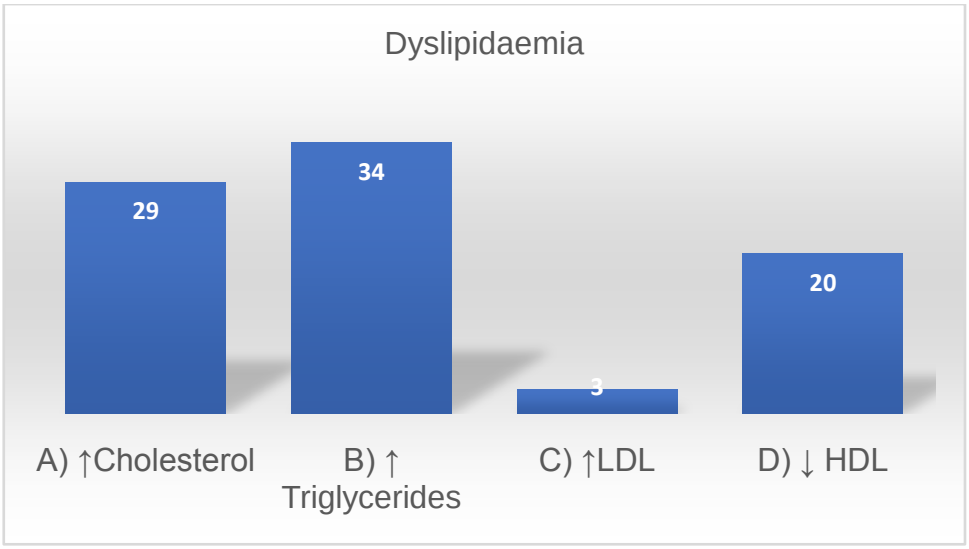

Figure No 6: Dyslipidemia In Children At The Time Of Enrolment

3. Thyroid status

In our study of 35 Children,9 Children (25.7 %) were found to be Hypothyroid and were started on thyroxine supplementation.

4. Genetics/ Family History:

In our study as there was no Family history, Genetic Testing was not done

5. Features Of Steroid Toxicity:

A) Cushingoid Habitus:

Table No .9(a): Features of Steroid Toxicity

Cushingoid	No. of cases	Percentage
YES	6	17.1%
NO	29	82.9%
Total	35	100.0%

In our study involving 35 SRNS children, 6 children had Cushingoid features (Truncal obesity, Moon Face, Striae) that is accounting for 17.1%.

B) Hypertension (New onset):

Table No .9(b): Features of Steroid Toxicity

Hypertension (New onset)	No. of cases	Percentage
NO	24	68.6%
YES	11	31.4%
Total	35	100.0%

In our study involving 35 SRNS children, 11 Children (31.4%) had New Onset Hypertension as a result of Steroid toxicity

6. Distribution Of Cases According To Histopathological Diagnosis:

Table No.10: Distribution of Cases According To Histopathological Diagnosis:

Renal Biopsy Findings	No. of cases	Percentage
MEMBRANOUS NEPHROPATHY	1	2.9%
ADVANCED GLOMERULOSCLEROSIS	1	2.9%
FSGS	10	28.6%
MCD	5	14.3%
MPGN	1	2.9%
NOT DONE	17	48.6%
Total	35	100.0%

Out of 35 children, Renal biopsy was done in 18 children; FSGS was present in 10 cases making it the predominant histopathological lesion (28.6% of all cases), MCD in 5 cases (14.3%), 1 Case each of Membranous Nephropathy, Membranoproliferative Glomerulonephritis and Advanced Glomerulosclerosis (2.9% each).

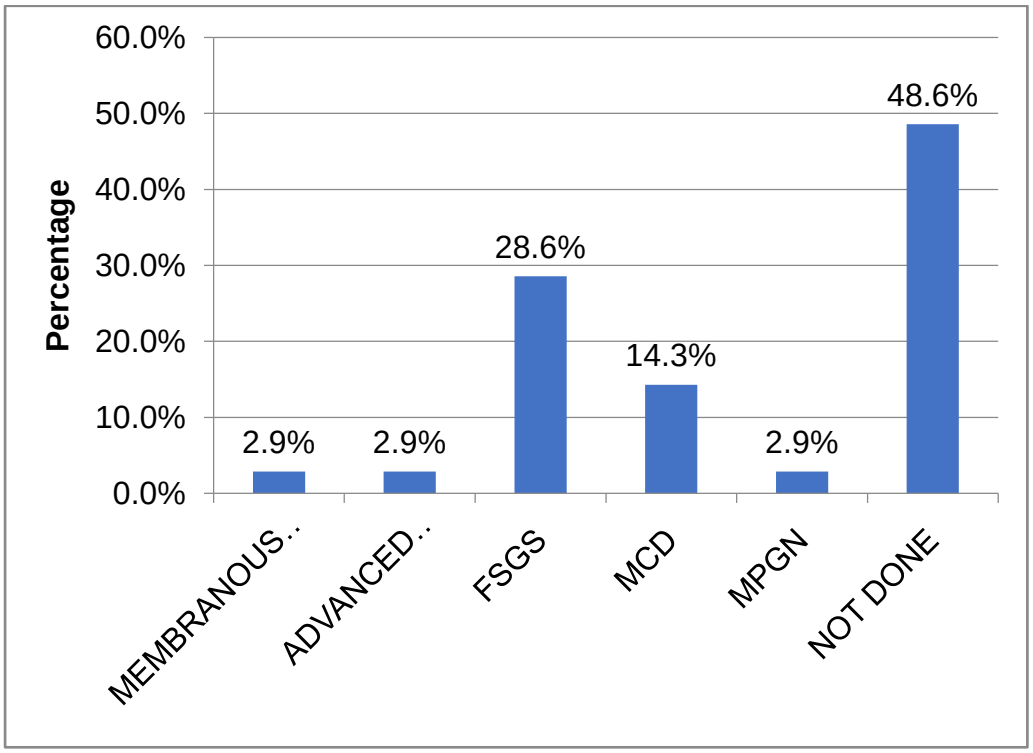

Figure No 7: Percentage of Children as Per Histopathological Diagnosis

Table No. 11: Distribution of FSGS Cases As Per Histopathological Variant

FSGS TYPE	Frequency	Percentage
TIP VARIANT	8	80.0%
NOS/CLASSIC VARIANT	2	20.0%
Total	10	100.0%

In Histopathological examination for FSGS, Tip variant was found to be the most common subtype (80%) with NOS/Classic variant comprising (20%).

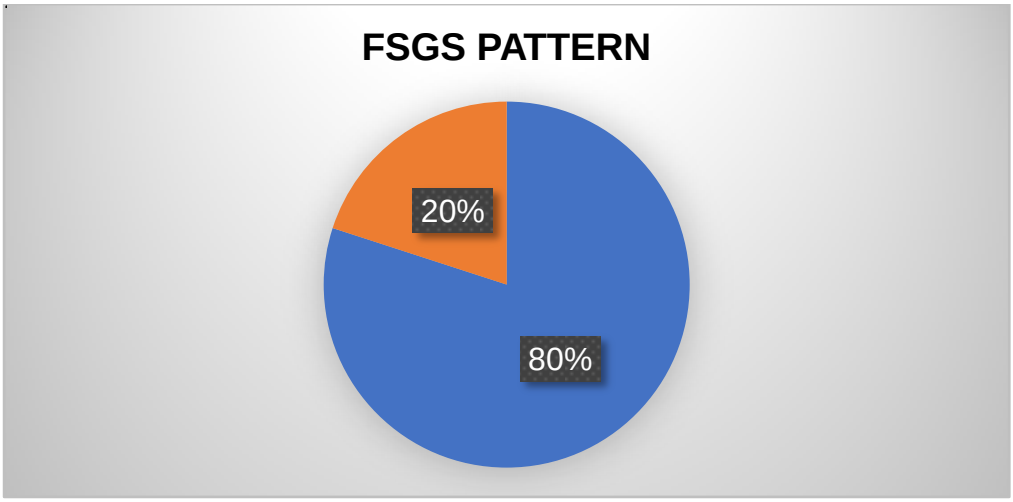

Figure No.8: Distribution of FSGS Cases as Per Histopathological Variant

7. Edema

Edema was there in all the 35 children enrolled in our study at presentation.

8. Baseline Proteinuria, Serum Albumin

Table No. 12: Mean Baseline Values of Spot UPCR And Albumin

	N	Mean	Std. Deviation	Min.	Max.
SPOT URINARY PROTEIN CREATININE RATIO	35	7.31	3.65	3.10	21.70
SERUM ALBUMIN	35	2.42	0.44	1.72	3.40

In our study of 35 Children,

1) Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio was 7.31± 3.65g/g.

2) Mean Serum Albumin was 2.42 ± 0.44 g/dl.

9. Status At 6 Months

A) Edema:

In our Study of 35 Children, Oedema was absent in 88.6% children (31/35), while it was present in 11.4% children (4/35).

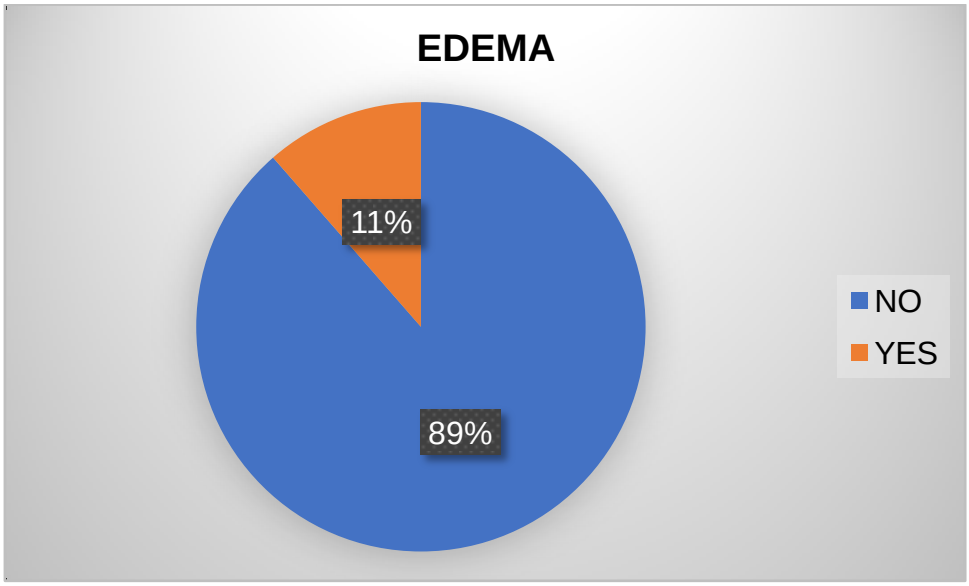

Figure No 9: Percentage of Children with Edema after 6 Months Of Therapy

B) Proteinuria, Serum Albumin

Table No. 13: Mean Values Of Spot UPCR And Serum Albumin After 6 Months Of CNI Therapy

	N	Mean	Stds Deviation	Min.	Max.
URINE PROTEIN CREATININE RATIO	35	0.97	1.28	0.11	4.40
SERUM ALBUMIN	35	3.16	0.40	2.01	4.00

In our study of 35 children,

1. Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio after 6 months of therapy with CNI was 0.97±1.28.

2. Mean serum albumin after 6 months of therapy with CNI was 3.16±0.4.

10. Primary Outcome

A) Complete Remission/ Partial Remission/ No Response

Table No. 14: Distribution of Cases as Per Complete Remission/ Partial Remission/ No Response

STATUS OF PATIENTS AT 6 MONTHS: CR/PR/NR	No. of cases	Percentage
CR	23	65.7%
PR	8	22.9%
NR	4	11.4%
Total	35	100.0%

In our study of 35 Children with SRNS who were given 6 months of CNI'S, 65.7% of them (23/35) achieved Complete remission, 22.9% (8) Partial remission and 11.4% (4) children were non responsive.

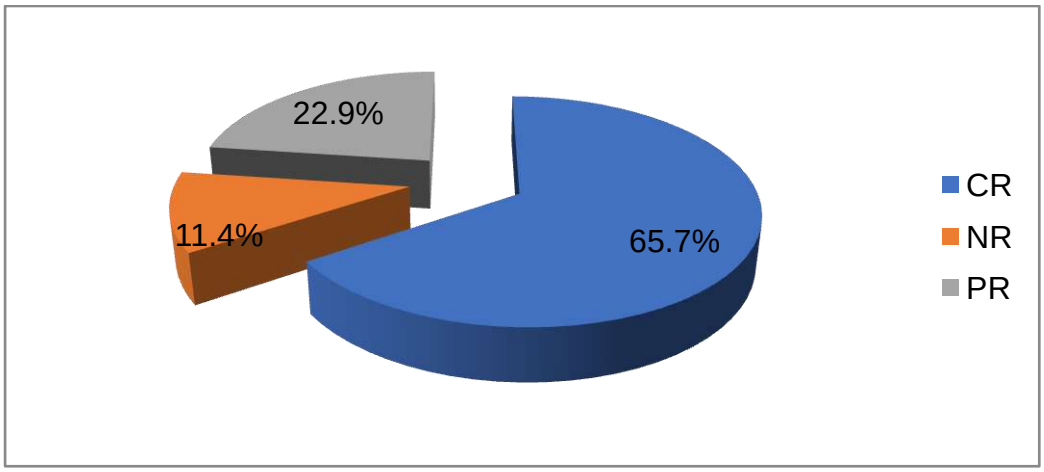

Figure No 10: Remission Status after 6 Months of Therapy

B) Response To Individual Cni

Table No. 15: Distribution of Cases as Per Response to Individual CNI

Drug Therapy	CR/PR/NR	Percentage (CR)
Cyclosporine	4/1/1	66.7%
Tacrolimus	19/7/3	65.5%

In our study group of 35 patients, 6 children (17.14%) received Cyclosporine and 29 children received Tacrolimus as first line therapy for SRNS, and CR was achieved in 4/6 (66.66%) and 19/29 (65.51%), respectively after 6 months of therapy.

11. TIME TO REMISSION

Table No. 16: Distribution of Cases as Per Time To Remission

Remission (Month)	No. of cases	Percentage
1^{ST}	24	68.6%
3^{RD}	28	80.0%
6^{TH}	31	88.57%
NR	4	11.4%

In our study of 35 Children with SRNS who were given 6 months of CNI'S, 68.6% of children (24/35) achieved Remission in 1^{st} Month, 80% of children (4/35) in 3^{rd} Month,88.57 % of children in 6^{th} Month (3/35), while 4 children were Non responsive (11.4%) at the end of 6 months.

12. Secondary Outcomes

A) Relapses

Table No. 17: Distribution of Cases as Per Number of Relapses after Starting CNI Therapy in 12 Months Period

No. Of Relapses After Starting Drug (In 12 Months Period)	No. of cases	Percentage
0	22	62.85%
1	7	20.0%
2	4	11.42%
3	2	5.7%
4	0	0.0%
5	0	0.0%
Total	35	100.0%

In our study of 35 children with SRNS who were given 6 months of CNI therapy, 37.14% children (13/35) had relapse within 1 year follow up of retrospective patients and last follow up visit of prospective/ new cases.

Table No. 18: Distribution of Cases as per number of relapses

Relapses	No. of cases	Percentage
NO	22	62.85%
YES	13	37.14%
Total	35	100.0%

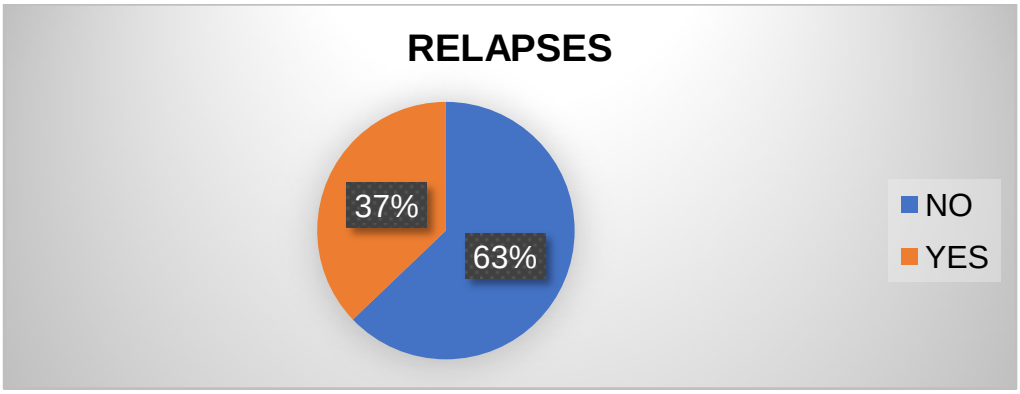

Figure No 11: Cases Who Had Relapses within 1 Year of Therapy

B) Side Effects Of CNI Therapy

Table No. 19: Distribution of Cases As Per Side Effects Of CNI Therapy

	No. of cases	Percentage
Hypertension (New onset)	16	45.7%
Hyperkalemia	0	0.0%
Seizure	0	0.0%
Increase Blood Sugar	0	0.0%
Increase OT/ PT	0	0.0%
Diarrhea	3	8.6%
UTI	5	14.3%
Reversible Nephropathy	0	0.0%
Hypertrichosis	0	0.0%
Gingival Hyperplasia	1	2.9%
Pneumonia	2	5.7%
Skin infections	0	0.0%

In our study of 35 children, Hypertension was the most common side effect in 45.7% (16/35) children, UTI in 14.3% (5/35), Diarrhoea in 8.6% (3/35), Pneumonia in 5.7% (2/35) and Gingival Hyperplasia in 2.9% (1/35) children.

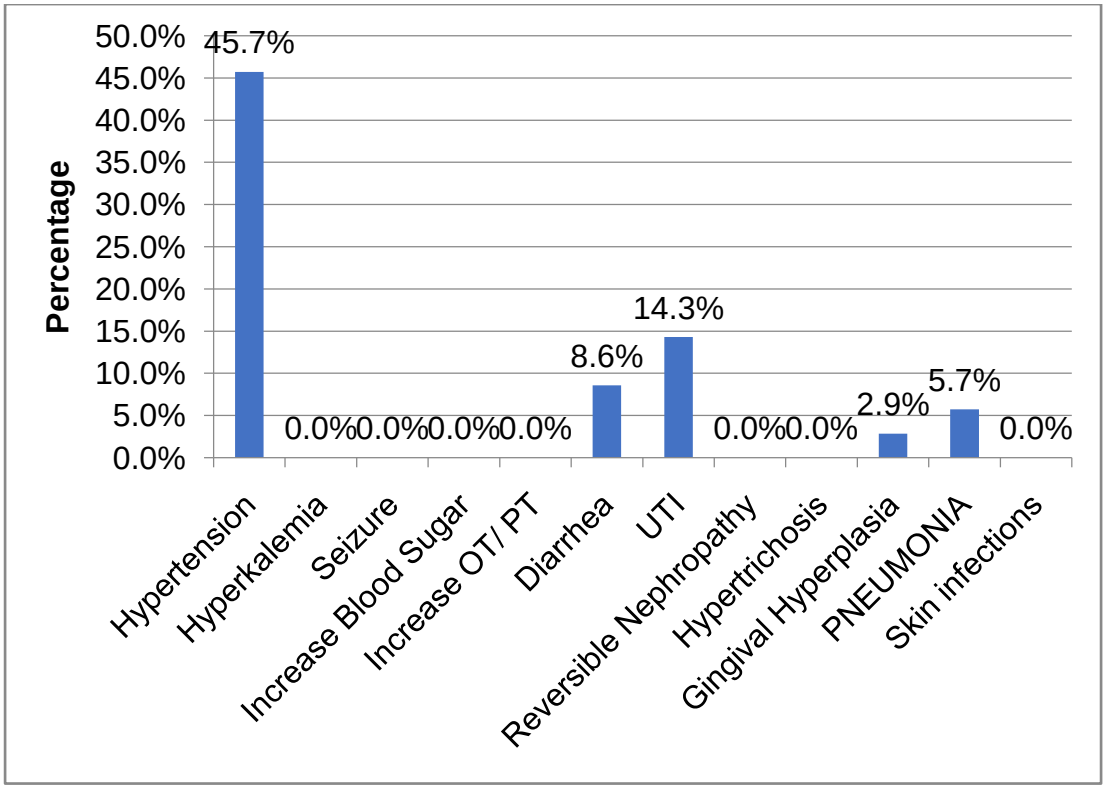

Figure No. 12: Side Effects of CNI Therapy

C) Renal Dysfunction

Of all the children in our study, 2 children were found to have renal dysfunction (eGfr<60ml/1.73m^2/min) defined as per Schwartz formula.

15) Status Of Children At Last Follow Up

Table No. 20: Distribution of Cases as Per Status of Children At Last Follow Up

STATUS OF PATIENTS AT LAST FOLLOW UP : CR/PR/NR	No. of cases	Percentage
CR	25	71.4%
NR	2	5.7%
PR	8	22.9%
Total	35	100.0%

Status of our study group children was noted during their last follow up visit in our study time period. It was found that 71.4% children (25/35) were in CR, 22.8% in PR (8/35) and 5.74% (2/35) were NR.

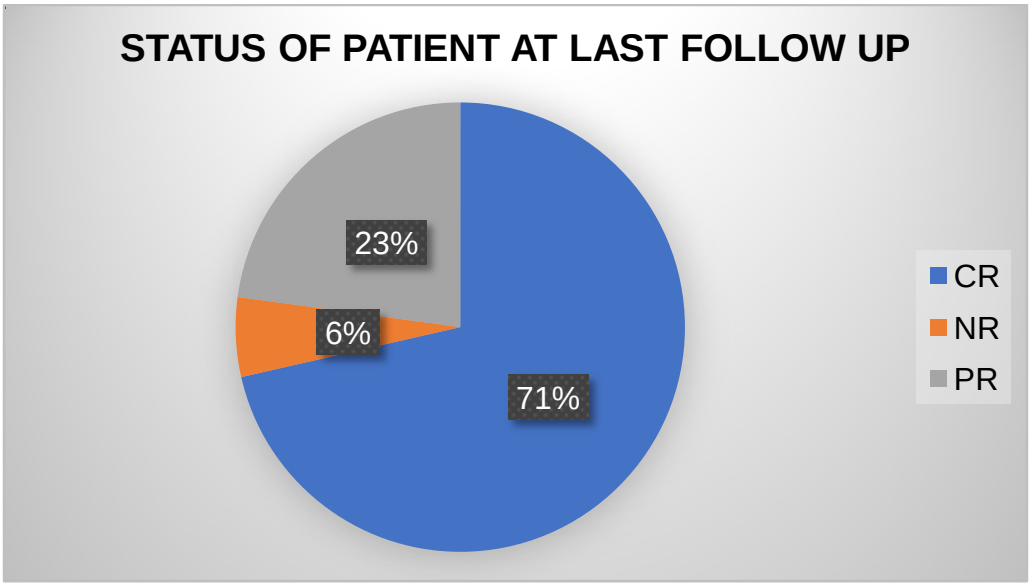

Figure No. 13: Status of Patient At Last Follow Up

16) Correlation Of Serum Albumin And Proteinuria At Baseline And At 6 Months Of CNI Therapy

Table No. 21(a): Correlation of Serum Albumin and Proteinuria at Baseline and At 6 Months Of CNI Therapy

	Mean	Std. Deviation	Std. Error Mean	T	p-value
SERUM ALBUMIN	2.42	0.44	0.08	-8.05	0.001
SERUM ALBUMIN AT 6 MONTHS OF CNI'S	3.16	0.4	0.07		

In our study of 35 children,

Mean serum albumin at baseline (2.42) was correlated with mean serum albumin after 6 months of therapy of therapy with CNI'S (3.16) and it was found to be statistically significant with p value of 0.001.

Table No. 21(b): Correlation of Serum Albumin and Proteinuria at Baseline and At 6 Months Of CNI Therapy

	Mean	Std. Deviation	Std. Error Mean	T	p-value
SPOT URINARY PROTEIN CREATININE RATIO	7.31	3.65	0.62	11.02	0.001
URINE PROTEIN CREATININE RATIO AT 6 MONTHS OF CNI'S	0.97	1.28	0.22		

In our study of 35 children,

Mean proteinuria measured as spot urine protein creatinine ratio at baseline (7.31) was correlated with mean spot urine protein creatinine ratio after 6 months of therapy of therapy with CNI'S (0.97) and it was found to be statistically significant with p value of 0.001.

17) Serum Albumin And Proteinuria At Baseline And At 6 Months Of CNI Therapy In Children Based On Renal Biopsy Done Or Not Done.

A) Baseline

1. Biopsied Children

Table No. 22: Mean Value Of Serum Albumin And Spot UPCR In Biopsied Children

Renal Biopsy	Yes	
	Mean	SD
SERUM ALBUMIN	2.47	0.44
SPOT URINARY PROTEIN CREATININE RATIO	6.45	2.49

Out of 35 children, renal biopsy was done in 18 children,

1) Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio of these 18 children was 6.45 ± 2.49g/g.
2) Mean Serum Albumin was 2.47 ± 0.44 g/dl.

2. Non- Biopsied Children

Table No. 23: Mean Value of Serum Albumin and Spot UPCR In Non-Biopsied Children

Renal Biopsy	No	
	Mean	SD
SERUM ALBUMIN	2.37	0.46
SPOT URINARY PROTEIN CREATININE RATIO	8.23	4.47

Out of 35 children, Renal biopsy was not done in 17 children

1) Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio of these 17 children was 8.23 ± 4.47g/g.

2) Mean Serum Albumin was 2.37 ± 0.46 g/dl.

B) 6 Months Of CNI Therapy

1) Biopsied Children

Table No. 24: Mean Value Of Serum Albumin And Spot UPCR In Biopsied Patients After 6 Months Of CNI Therapy

Renal Biopsy	Yes	
	Mean	SD
URINE PROTEIN CREATININE RATIO at 6 months	0.96	1.30
SERUM ALBUMIN at 6 months	3.05	0.39

Out of 35 children, renal biopsy was done in 18 children,

A) Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio of these 18 children after 6 months of CNI therapy was 0.96 ± 1.30 g/g.

B) Mean Serum Albumin after 6 months of CNI therapy was 3.05 ± 0.39 g/dl.

2) Non- Biopsied Children

Table No. 25: Mean Value Of Serum Albumin And Spot UPCR In Non-Biopsied Patients After 6 Months Of CNI Therapy

Renal Biopsy	No	
	Mean	SD
URINE PROTEIN CREATININE RATIO at 6 months	0.99	1.29
SERUM ALBUMIN at 6 months	3.29	0.39

Out of 35 children, renal biopsy was not done in 17 children,

A) Mean daily urinary protein excretion measured as Spot Urine protein creatinine ratio of these 17 children after 6 months of CNI therapy was 0.99 ± 1.29 g/g.

B) Mean Serum Albumin after 6 months of CNI therapy was 3.29 ± 0.39 g/dl

C) Correlation of proteinuria and serum albumin at baseline and at 6 months of CNI therapy in biopsied and non – biopsied.

Table No. 26: Correlation Of Proteinuria And Serum Albumin At Baseline And At 6 Months Of CNI Therapy In Biopsied And Non – Biopsied

Renal Biopsy	Yes		NO		Z	p-value
	Mean	SD	Mean	SD		
Difference between SERUM ALBUMIN baseline to 6 months	-0.58	0.46	-0.92	0.59	-1.884	0.068
Difference between SPOT URINARY PROTEIN CREATININE RATIO baseline to 6 months	5.49	2.73	7.25	3.88	1.557	0.129

In our study of 35 children,

1) The correlation between serum albumin at baseline and at 6 months of CNI therapy was studied and was found to be statistically insignificant in both biopsied and not biopsied children with p value of 0.068.

2) The correlation between proteinuria measured as spot UPCR at baseline and at 6 months of CNI therapy was studied and was found to be statistically insignificant in both biopsied and not biopsied children with p value of 0.129.

18) Patient characteristics by response to CNI'S

Table No. 27: Patient Characteristics by Response To CNI's

	CR/PR		NR		Z	p-value
	Mean	SD	Mean	SD		
Age Of Onset	3.87	2.40	3.43	1.06	0.364	0.719
Serum albumin	2.48	0.44	1.97	0.18	-2.205	0.027
UPCR	6.82	2.77	11.13	7.22	-2.371	0.024

Table No. 28: Patient Characteristics By Response To CNI's

6-month status						Total	Chi-square value	p-value
		CR/PR		NR				
Sex	F	8	25.80%	2	50.00%	10	1.016	0.313
	M	23	74.20%	2	50.00%	25		
Drug Given	Cyclosporine	5	16.10%	1	25.00%	6	0.196	0.658
	Tacrolimus	26	83.90%	3	75.00%	29		
Renal Biopsy Findings	MEMBRANOUS NEPHROPATHY	1	3.20%	0	0.00%	1	0.133	0.715
	ADVANCED GLOMERULOSCLEROSIS	1	3.20%	0	0.00%	1	0.133	0.715
	FSGS	8	25.80%	2	50.00%	10	1.016	0.313
	MCD	5	16.10%	0	0.00%	5	0.753	0.386
	MPGN	1	3.20%	0	0.00%	1	0.133	0.715
	NOT DONE	15	48.40%	2	50.00%	17	0.004	0.952

Out of 35 children included in our study, age of onset of disease, sex, drug distribution and type of histopathology did not have a significant difference, while there was a statistically significant difference between serum albumin and spot UPCR between CR/PR & NR.

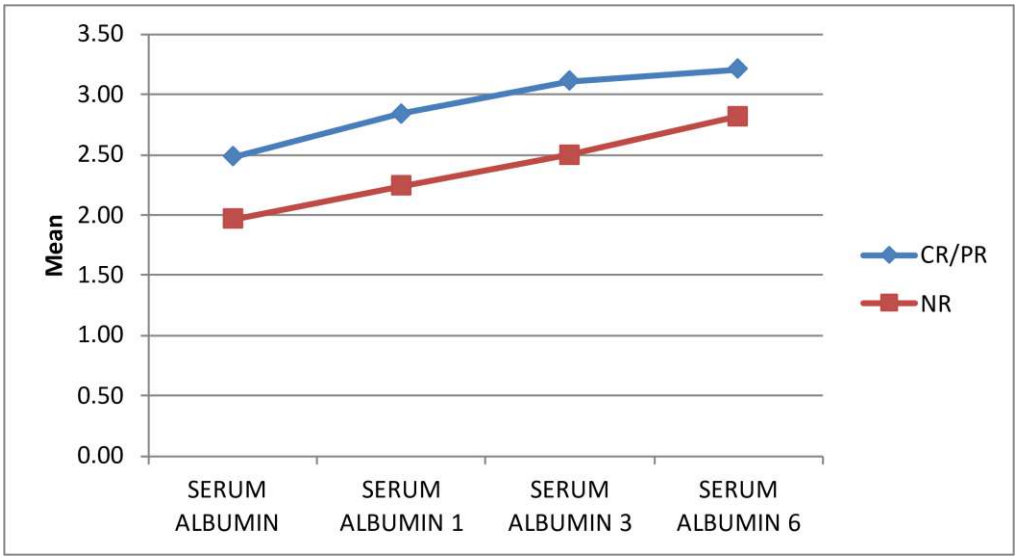

Figure No.14: Serum Albumin In CR/PR And NR Children At Baseline, After 1,3 And 6 Months Of CNI Therapy

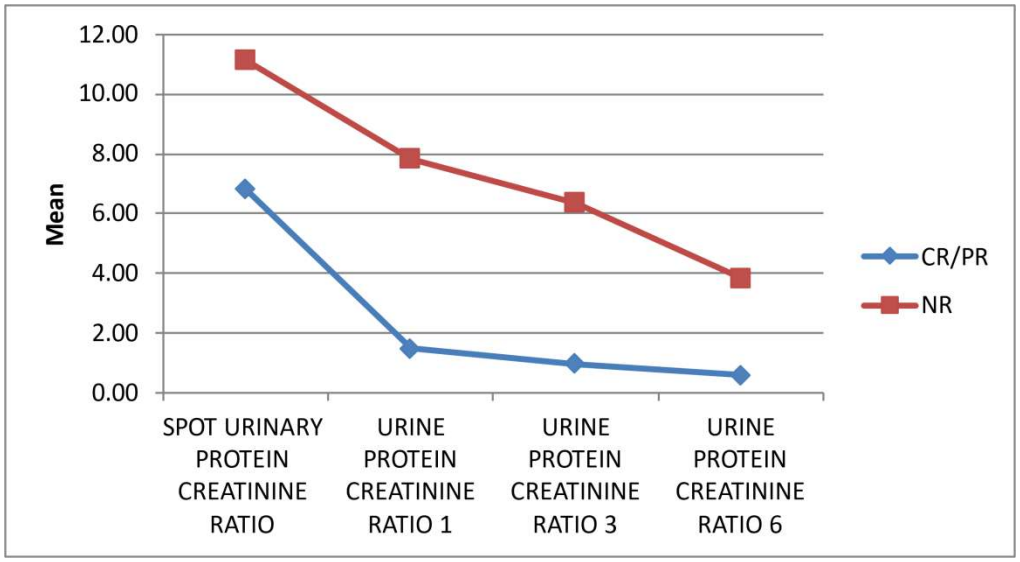

Figure No 15: Spot Urinary Protein Creatinine Ratio In CR/PR And NR Children At Baseline, After 1,3 And 6 Months Of CNI Therapy

19) Patient Characteristics By Response To CNI's In Biopsied And Non-Biopsied Children

Table No 29 (a): Patient Characteristics by Response To CNI's In Biopsied And Non-Biopsied Children

Renal Biopsy	NO		Yes		Z	p-value
	Mean	SD	Mean	SD		
Age Of Onset	4.09	2.48	3.57	2.11	0.671	0.507
SERUM ALBUMIN	2.37	0.46	2.47	0.44	-0.623	0.537
SPOT URINARY PROTEIN CREATININE RATIO	8.23	4.47	6.45	2.49	1.474	0.15

Table No 29 (b): Patient Characteristics by Response to CNI's In Biopsied And Non-Biopsied Children

Renal Biopsy						Total	Chi-square value	p-value
		NO		Yes				
Sex	F	5	29.40%	5	27.80%	10	0.011	0.915
	M	12	70.60%	13	72.20%	25		
Drug Given	Cyclosporine	2	11.80%	4	22.20%	6	0.673	0.412
	Tacrolimus	15	88.20%	14	77.80%	29		
STATUS OF PATIENTS AT 6 MONTHS: CR/PR/NR	CR	11	64.70%	12	66.70%	23	0.015	0.993
	NR	2	11.80%	2	11.10%	4		
	PR	4	23.50%	4	22.20%	8		

Out of 35 children included in our study, age of onset of disease, sex, serum albumin, spot UPCR, drug distribution and remission status did

not have a significant difference between biopsied and not biopsied children.

20) Major Infections Requiring Hospitalisation

Table No 30: Major Infections Requiring Hospitalisation

Major infection (Requiring hospitalization) Diagnosis	No. of cases	Percentage
NO	29	82.9%
BRONCHIOLITIS	1	2.9%
URI	1	2.9%
UTI	1	2.9%
PNEUMONIA	2	5.7%
PRESS	1	2.9%
Total	35	100.0%

Out of 35 children enrolled in our study, 2 children developed Pneumonia (5.7%), 1 case each of Bronchiolitis, UTI, URTI and PRESS (each accounting 2.9%).

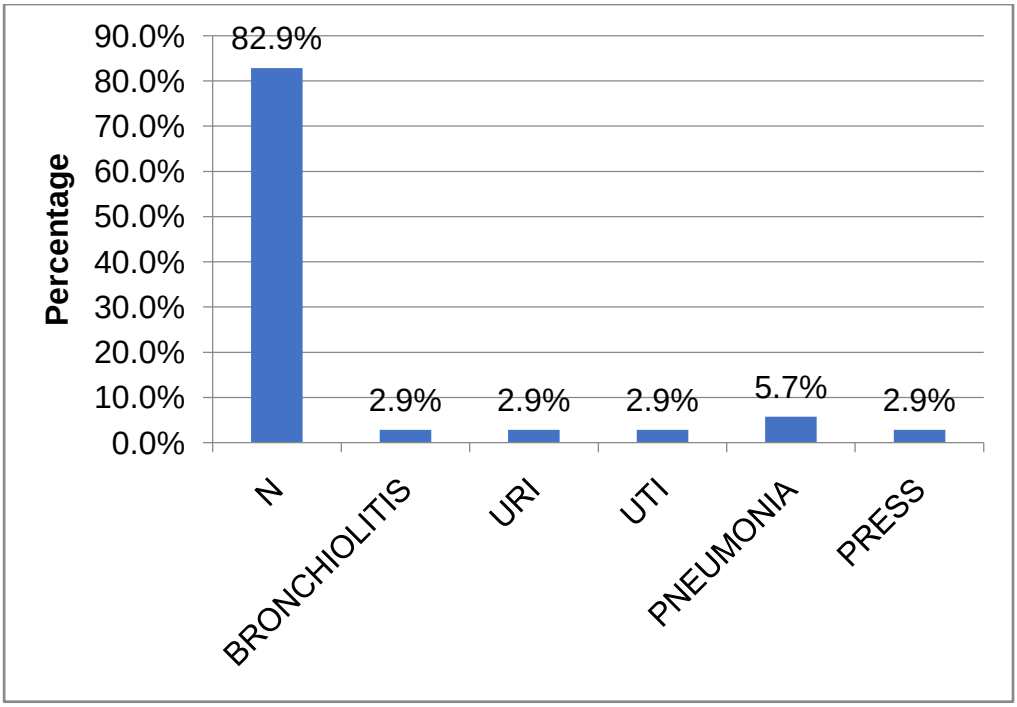

Figure No. 16: Major Infections Requiring Hospitalisation

21) Change Of Therapy

Table No 31(a): Change Of Therapy

Change of Therapy	No. of cases	Percentage
NO	32	91.4%
YES	3	8.6%
Total	35	100.0%

Table No 31(b): Type of Therapy

Drug Started (Rituximab)/Cyclophosphamide (Y/N)	No. of cases	Percentage
NO	32	91.4%
YES	3	8.6%
Total	35	100.0%

Table No. 32: Response to Change Of Therapy

Response At 6 Months Post Rituximab/Cyclophosphamide (CR/PR/NR)	No. of cases
CR	2
PR	1
NR	0
Total	3

In 3 (8.6%) out of 35 children, therapy was changed due to no response. Children were given Rituximab or Cyclophosphamide. Out of these 3 children, 2 had CR and 1 had PR.

DISCUSSION

This study was done in the Department of Nephrology and Paediatric Nephrology on children attending OPD of Dayanand Medical College, Ludhiana. It was an observational study of both retrospective and prospective cases during study period from Aug, 2021 to May, 2022.

The retrospective cases included previously diagnosed SRNS children coming to OPD for follow up within the study period. The prospective cases included newly diagnosed SRNS children (Within study period) with 6 months of follow up.

Though various studies have been done which have reported the outcomes with the use of CNI's in children with SRNS, the information on long-term outcomes from India is still lagging. [44, 45, 46]

Most guidelines recommend treatment of SRNS with CNI's for a duration of 2 to 3 years. [1, 47] The disease course changes with the treatment, and the outcomes depend upon achievement of prolonged remission and drug toxicity with prolonged use of CNI's. Ethnicity and genetics of SRNS also influence the long-term outcomes. [5, 6]

Of all the children attending Nephrology and Paediatric Nephrology Clinic of Dayanand Medical College and Hospital, 35 children met the inclusion criteria.

Out of 35 children, 25 children (71.4%) were retrospective cases and 10 were (28.6%) prospective.

Treatment Regimen

CNI therapy, with drugs Cyclosporine & Tacrolimus, was given to these children. 29 children (82.9%) were given Tacrolimus and 6 (17.1%) were given Cyclosporine.

Tacrolimus was preferred to cyclosporine except in children who were

unable to swallow tablets.

Age Distribution:

In our study maximum number of children at the time of enrolment (22) were in the age group of 6-12 years accounting for 62.9% of all cases with most common age of presentation between 2-8 years (80%).

The mean age of onset of Nephrotic syndrome in our study was 3.82±2.28 years. Similar study done by Agrwal S et al [43]showed mean age at the onset of nephrotic syndrome being 48 (24–87) months.In a similar study done by Inaba et al [20] the mean age was found to be 3.2 years.

In contrast, Mean age of onset of 5.4 years was found in astudy conducted by Sehrawat KS et al [48] Similarly, study done by Butani et al [37] had mean age of presentation 5.2 (2-13.3) years. The onset of disease in a study conducted by Om P Mishra et al [49] also showed similar results of onset of disease between 1–5 years (median 4.5 years). Trautmann et al [32] reported similar incidence of SRNS between 1–5 years, and Mekahli et al [50] found similar median age in their study subjects. Ali et al [35] reported that 29.2% of the sample had age of onset of SRNS between 1–5 years of age and 46.5% between5–10 years of age.

Sex Distribution:

Our study constituted 25 males and 10 females. There was male predominance in our study (71.4%).The Male: Female ratio was 2.5 :1. Similarly White et al [51] also reported a male to female ratio 2:1in their study. Srivasthava et al [52] reported a male to female ratio of 3:1 in younger children and 7:1 in older children. Male predominance (79.1%) was also seen in study conducted by Agrwal S et al [43] A similar study by Mutalik et al [53] showed male predominance with a male-to-female

ratio of 1.2:1.In a similar study conducted by Mishra OP et al [49] the male: female ratio was 1.8:1, which is in accordance with the reports of other authors (1.4–1.9:1). [20, 50]

Body Mass Index

In our study group of 35 children, 22 children (62.8%) were having normal BMI (5^{th}-85^{th} percentile), 9 children (25.71%) were Obese (>95^{th} percentile), 3 children (8.5%) were under-weight (< 5^{th} percentile) & 1 (2.8%) was overweight; defined as per CDC guidelines.

Regional Distribution:

In our study group, there were 27 Urban and 8 Rural children accounting for 77.1% Urban children, showing Urban Predominance. Similar predominance in urban settings was found in a study conducted by Sehrawat KS et al. [48]

Steroid Related Side effects:

1. Cushingoid features were observed in 17.1% of our patients (6/35)
2. Hypertension was observed in 31.4% of our patients (11/35)

Associated findings:

Features like haematuria, hypertension and renal failure are found to be more common in steroid resistant nephrotic syndrome. The reason behind this may be that SRNS produces structural damage to the kidney unlike MCN where the basic pathology is only the loss of negatively charged glycosaminoglycans.

Hypertension at the onset was documented in 4 of children with resistance. We found hypertension in 11.42 % of the patients of SRNS. There is a wide contrast in the reported prevalence of hypertension in the cases of childhood nephrotic syndrome ranging from 8 to 59.1% [54]

there are multiple reasons to it, at the centre of which is the multiple definitions of hypertension in these studies. Various attributable factors include medications such as steroids and cyclosporine and tacrolimus, all of which increase the risk for developing hypertension. [55] As hypertension has long-term cardiovascular risk and bearing on renal outcomes, close monitoring of BP is recommended. Similar study by Mekahli et al [50] reported Hypertension in 8% cases, while study by Ali et al [20] reported Hypertension in 48% children.

Microscopic Haematuria was present in 2 children (5.7%) in the present study.In contrast, studies conducted by Ali et al [20] and Mekhali et al [50] reported microscopic haematuria in 57% of all cases.

Dyslipidaemia

In our study group of 35 children, Hypertriglyceridemia was found in 97.14% children (34/35), Hypercholesterolaemia in 82.86% children (29/35), Low HDL in 57.14% children (20/35) & Increased LDL in 8.57% children (3/35).

Hypothyroidism

Hypothyroidism was detected in 25.7% of all cases.Similarly, study conducted by Kapoor K et al [56]& Singh S et al [57] reported incidence of hypothyroidism in 20–26.2% of SRNS patients and most of the cases had subclinical hypothyroidism. Loss of proteins in urine, such as thyroid binding protein, pre-albumin, and albumin, result in decreased level of serum protein, thyroglobulin, and T3 levels. The children with hypothyroidism may need thyroxine supplementation to achieve remission.

Renal Biopsy

Underlying histopathology also influences the clinical presentation and the outcomes of children with SRNS. Renal biopsy was done in 18 children showing predominance of FSGS in 55.55% cases (10/18), Minimal change disease in 5/18 children (27.77%), Membranous Nephropathy in 1/18 children (5.55%), Advanced Glomerulosclerosis in 1/18 children (5.55%) and MPGN in 1/18 children (5.55%).

Similarly, study done by Banaszak et al [58] compared the histopathology of childhood nephrotic syndrome over two consecutive decades (1985– 1995 and 1996–2005) and reported a tendency toward increasing proportional incidence of FSGS and fall in the incidence of MCD.

Also, a study done by Gulati S et al [59] showed Focal segmental glomerulosclerosis (FSGS) to be the commonest 80/136 (59%), followed by MCD (17.6%).In 2005, an Indian study reported FSGS tobe the most common histopathological finding in children with SRNS accounting for 59% of the total cases. [22] A higher incidence of FSGS was further reported in later studies. A randomized controlled trial (RCT) from India reported the incidence of FSGS and MCD as 69% and 31%, respectively. [33]

A higher incidence of FSGS was also reported by the PodoNet registry (primarily European countries) data that looked at SRNS in children (n= 1,368) and documented a higher proportion of FSGS (56%) compared with MCD (21.1%).

Previously, MCD was reported as the most common cause of NS in children. But in the last two decades, there has been an apparent surge in the incidence of FSGS. It may be explained by improved diagnosis of FSGS on kidney biopsy most likely due to guided biopsies which give a better yield of tissue translating to more number of

glomeruli being examined and hence more chances of detecting FSGS. Ubiquitous environmental factor or factors with a possible genetic predisposition may also be contributing to such change. [60]

The histopathological lesion in SRNS influences the response to immunosuppressive therapy. The variability in histopathological lesions in patient with SRNS can occur from region to region which may affect long term outcomes.

TREATMENT OUTCOMES

PRIMARY OUTCOME (Remission after 6 Months of CNI therapy)

Achieving remission in children with SRNS is difficult, and many immunosuppressive drugs have been used with variable success. CNI's are the preferred drugs for treatment of childhood SRNS [61,62] Treatment outcomes were measured in response to CNI's as Complete Remission, Partial Remission and No Response.

In our study, 65.7 % of children attained CR, 22.9% attained PR & 11.4% children were non responsive to CNI after 6 months of therapy.

Similarly, study conducted by Agrwal S et al [43] showed achievement of CR with CNI's in 69.2% children. In a study conducted by Mishra OP et al [49] 57.3% of children achieved remission with CNI therapy.

Of all the children, who received Cyclosporine, CR was achieved in 66.7% & who received Tacrolimus, CR was observed in 65.5% of them.

In a study conducted by Choudhry S et al [17] after 6 months of therapy, remission occurred in 18 (85.7%) and 16 patients (80%) treated with tacrolimus and CsA, respectively. In a study conducted by Prasad N et al [33] After 6 months of treatment, 16/23 (69.5%) patients on CSA achieved remission and 18/22 (81.8%) on TAC achieved

remission (*P* = 0.3).

In a study conducted by Agrwal S etal [43] Calcineurin inhibitors (CNI's) were used in 86.8% of the children, and response rates with cyclosporine and tacrolimus for complete remission (CR) were 80% and 73.7%, respectively. The results of our study was also in correlation with study done by Inaba A et al [20]

Previously, different rates of complete remission (30–45.2%), partial remission (13–19.3%), and total remission (49 to 83%) have been reported by different authors depending on the selection criteria. [20, 32, 50, 63]

Patient Characteristics by Response to Immunosuppression

The various factors studied for overall remission were age of onset of disease,sex, serum albumin, Spot UPCR, drug distribution and histopathology.

The mean age of onset of children achieving CR/PR& NR was 3.87±2.4& 3.43±1.06 respectively. This was statistically insignificant and was in correlation with Trautmann et al [32] who did not find any significant difference in the age of onset of the children achieving CR, PR, or NR. A similar study done by Mishra OP et al [49] showed the same results.

There was no significant statistical difference between children achieving CR/PR & NR on the basis of gender. This was similar to study done by Agrwal S et al [43] which showed that there was no significant association of gender with the remission rate.

The mean serum albumin and spot UPCR levels at baseline were compared and found to be statistically significant in remission and non-remission group. The results of our study were similar to study done by

Mishra OP et al. [49]

In our study group, there was no statistically significant difference between therapy with cyclosporine and tacrolimus in achieving remission. The results of our study aresimilar to study done by Agrwal S et al. [43]

In present study renal biopsy was done in 18 children. There were 10 cases of FSGS, 5 of MCD, and 1 case each of membranous nephropathy, advanced glomerulosclerosis and MPGN. However statistically no significance (p value 0.313) was found for remission status after 6 months of CNI therapy in relation to histology. This was in accordance with study done was Mishra OP et al. [49]

Genetic diagnoses were identified in 23.6% of the children with SRNS in the PodoNet registry, and chances of detecting a genetic etiology reduced with increasing age (35.6% in children 3–12 months of age compared with 15.6% in children 6–11 years of age). Only 10.4% of these children responded to immunosuppressive therapy. [44] It is possible that in our study, some of the children with NR had underlying genetic etiology, although this could not be ascertained as no genetic testing was done. RCTs and cohort studies show that therapy with cyclosporine or tacrolimus results in CR in 30% to 40% and CR or PRin 60% to 80% of patients. [14, 17]

Attaining PR is an important predictor for a good outcome in children with SRNS; the risk of ESKD decreases by 85% to 90% if CR was achieved and by 50% for those with PR. Ten-year renal survival rates were 94% and 72%, respectively, for those with CR and PR, and only 43% for those with NR to immunosuppression in one cohort. [32]

Patient Characteristics by Response to Immunosuppressive In Biopsied and Non- Biopsied Children

In our study of 35 children, age of onset of disease, sex, serum

albumin, spot UPCR, drug distribution and remission status did not have a statistical significant difference between biopsied and not biopsied children.

SECONDARY OUTCOMES

1. **Relapse**

In our study, 37.14% children had relapse within 12 months of starting of CNI therapy. Similarly, study conducted by Wang W et al [54] found relapse rate of 36% within 1 year of CNI therapy.

2. **Side Effects Of CNI Therapy**

Side effects observed were hypertension, UTI, diarrhoea, Pneumonia, and gingival hyperplasia in 45.7%, 14.3%, 8.6%,5.7% and 2.9% of cases, respectively.

Similarly, Inaba et al [20] reported hypertension in 31.9%, short stature in 7.2%, and obesity in 5.8% of cases. Ali et al [35] reported drug-related complications such as cushingoid appearance (9.2%), hirsutism and Gingival hypertrophy (2.3%) and short stature (1.5%). Therefore, attention should also be paid to such adverse-effects during treatment and managed accordingly.

3. **Renal Dysfunction**

In our study, 2 patients who were NR had deranged renal function (eGfr<60ml/1.73m^2/min) defined as per Schwartz formula as the last follow up accounting for 5.71%. This result is similar to study done by AgrwalS et al [43] which showed that four children out of 91 (4.4%) developed Renal dysfunction/progressed onto CKD.

Table No. 33: Comparison of Our Study with Other Studies

Study	No	Age of onset (yrs.)	M/F	Regional distribution (U/R)	Clinical Profile	Histopathology (Predominant)	CR/PR/NR	Relapses	Side effects
					Hypertension/ Microscopic Hematuria				Hypertension/ UTI/Diarrhea/ Gingival Hyperplasia
Our study	35	3.82 ±2.28	2.5:1	77.14%/22.87%	11.4%/ 5.7%	FSGS	65.7%/ 22.9%/ 11.4%	37.14%	45.7%/ 14.3%/ 8.6%/ 2.9%
Sinha et al (2017)	31	4.1	2.8:1	-	- / -	MCD	74.19% / 16.12%/ 9.69%	45.20%	-/-/22.5%/ -
Prasad et al (2018)	45	8.52 ±0.071	95.55 (43)% /4.45 % (2)	-	-/ -	FSGS	53.25%/ 22.4%/ 24.35%	17%	- / - / 9.09% /30.43%
Chen et al (2020)	76	7±3	2.30: 1	-	- / -	Ms PGN	93.4%/ 2.6%/ 4%	39.70%	NONE

Major Infections after CNI Therapy

During therapy, a few patients had major infections requiring hospitalization in our study. In the present study 2 patients had pneumonia and there were of 1 case each of URI, UTI, PRESS and Bronchiolitis.

Change of Therapy

The therapy was changed to Rituximab and Cyclophosphamide in 3 patients due to no response/ side effects to CNIs. Two out of them got complete remission and 1 had partial remission.

Limitations

A major limitation of this study was smaller number of patients. This is mainly because of loss of follow up and missing records. The covid 19 pandemic was also one of the major factors in the limiting the number of children visiting the hospital OPD.

Due to financial restrains and the non-availability in our centre, the genetic testing was not performed. However, the family history was not there in any of our cases.

Taking into consideration that SRNS is a rare disease in childhood and this study being a single-centre study, these limitations are not completely avoidable.

SUMMARY AND CONCLUSION

- The present study was conducted in Nephrology clinic of a tertiary care hospital, DMCH Ludhiana on patients between 3 months to 18 years of age who were newly diagnosed SRNS cases or who were already known case of SRNS and were on immunosuppressants for at least 6 months.

- Total 35 patients were included in the study, 25cases were already diagnosed SRNS cases on follow up and 10 were newly diagnosed during study period from Aug, 2021 to May, 2022.

- The maximum number of children (22) at the time of enrolment were in the age group of 6-12 years. The Mean age of Onset of Nephrotic Syndrome in our study was 3.82±2.28 years.

- In the present study, there were 25 male children and 10 female children showing male predominance.

- There were 27 Urban and 8 Rural children in our study showing Urban Predominance.

- Out of 35 Children, 22 out of 35 children (62.8%) were having normal BMI, 9 were Obese (25.71%), 3 were underweight (8.5%) and 1 was overweight (2.8%); defined as per CDC guidelines.

- Out of 35 children, 4 Children presented with Hypertension at Onset (11.4 %), 2 (5.7%) had microscopic hematuria.

- Out of 35 children, 9 children (25.7%) were found to be hypothyroid.

- Out of 35 children, Renal biopsy was done in 18 children; FSGS was present in 10 cases making it the predominant histopathological lesion (28.6% of all cases), MCD in 5 cases (14.3%), 1Case

each of Membranous Nephropathy, Membranoproliferative Glomerulonephritis , and Advanced Glomerulosclerosis (2.9% each).

- 29 children were given Tacrolimus and 6 children were given cyclosporine

- In our study of 35 Children with SRNS who were given 6 months of CNI's, 65.7% of them (23/35) achieved Complete remission, 22.9% (8) achieved partial remission and 11.4% (4) childrenwere non responsive.

- Out of all 35 children in the present study, 6 children (17.14%) received Cyclosporine and 29 children received Tacrolimus (82.85%) as first line therapy for SRNS ; and CR was achieved in 4/6 (66.66%) and 19/29 (65.51%), respectively after 6 months of therapy.

- Children with SRNS who were given 6 months of CNI'S, 68.6% of them (24/35) achieved Remission in 1st Month, 80% of children (28/35) in 3rd Month,88.57 % of children in 6th Month (31/35), while 4 children were Non responsive (11.4%) at theend of 6 months.

- In our study of 35 children with SRNS who were given 6 months of CNI therapy, 37.14% children (13/35) had relapse within 1 year follow up of retrospective patients and last follow up visit of prospective/ new cases.

- Hypertension was found to be the most common side effect in our study, in 45.7% (16/35) children followed by UTI in 14.3% children (5/35), Diarrhea in 8.6% (3/35), pneumonia in 5.7% (2/35)and Gingival Hyperplasia in 2.9% (1/35) children.

- Of all the children in our study, 2 children were found to have renal dysfunction (eGfr<60ml/1.73m^2/min) defined as per Schwartz formula.

- Out of 35 children included in our study, age of onset of disease, sex, type of CNI given and renal histopathology did not significantly differ

between remission and non-remission patients. However, there was statistically significant difference between serum albumin and spot UPCR in remission and non- remission groups.

- Out of 35 children included in our study, age of onset of disease, sex, serum albumin, spot UPCR, drug distribution and remission status did not have a significant difference between those were biopsied and those were not.

- Out of 35 children enrolled in our study, 2 children developed Pneumonia (5.7%), 1 case each of Bronchiolitis, UTI, URTI and PRESS (each accounting 2.9%) which required hospitalization.

- In 3 (8.6%) out of 35 children, therapy was changed due to no response. Children were given Rituximab or Cyclophosphamide. Out of these 3 children, 2 had CR and 1 had PR.

CONCLUSION

- The present study was conducted and included 35 children who were identified to have SRNS. CNI's were started in all children. There was good response in majority of the children. Renal biopsy was done in 18/35 children and it was found out that renal biopsy did not have any bearing on the outcome. Though it was a small study with remission in 88.6% children, CNI's have a good response in majority of the children.

- To conclude, we recommend CNI'S as 1st line of therapy for treatment of SRNS and need monitoring of renal function tests to avoid permanent nephrotoxicity. We further recommend starting a CNI in SRNS without waiting for renal biopsy.

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Sl. No.	Follow Up/ New	Drug Given	Name	Current Age (In years)	Sex (MALES(M)/FEMALES(F))	Date of birth	Weight At Start of Therapy(Kgs)	Height at start of Therapy (cm)	BMI	BMI GROUP
1	Follow Up	Tacrolimus	R.K	7	F	15-12-2014	13	90	14.7	Normal
2	Follow Up	Tacrolimus	R	5	M	09-07-2016	12.3	85	17	Normal
3	Follow Up	Tacrolimus	M.S	8	M	19-08-2013	20.5	115	15.5	Normal
4	Follow Up	Tacrolimus	S.S	3	M	21-01-2018	11	92	13	Underweight
5	Follow Up	Tacrolimus	G.K	11	F	22-04-2010	24.1	121	16.5	Normal
6	Follow Up	Tacrolimus	B.K	6	M	15-06-2015	16	101	15.7	Normal
7	Follow Up	Tacrolimus	K.K	8	M	24-10-2013	16.6	103	15.6	Normal
8	Follow Up	Tacrolimus	P.S	11	M	11-06-2010	44	114	33.9	Obese
9	Follow Up	Tacrolimus	W.S	8	M	24-08-2013	20	98	20.8	Obese
10	Follow Up	Tacrolimus	J.S	7	M	30-06-2014	16.7	93	19.3	Obese
11	Follow Up	Tacrolimus	K.S	5	M	10-02-2016	18.5	99.5	18.7	Normal
12	Follow Up	Tacrolimus	G.S	7	M	20-01-2014	18.5	113	14.5	Normal
13	Follow Up	Tacrolimus	A.S	6	M	02-11-2015	17	103	16	Normal
14	Follow Up	Tacrolimus	B.K	12	F	09-06-2009	15	90	18.5	Normal
15	Follow Up	Tacrolimus	R.K	6	M	07-10-2015	12	92	14.2	Normal
16	Follow Up	Tacrolimus	M.K	6	F	30-12-2015	20	99	20.4	Obese
17	Follow Up	Tacrolimus	M.S	10	M	21-06-2011	15	92	17.7	Normal
18	Follow Up	Tacrolimus	G.K	3	F	25-08-2018	12	86	16.2	Normal
19	Follow Up	Tacrolimus	K.A	7	M	13-10-2014	15	90	18.5	Obese
20	Follow Up	Cyclosporine	S.S	14	M	16-11-2007	12.7	91	15.3	Normal
21	Follow Up	Cyclosporine	R.K	9	M	18-11-2012	13.4	86	18.1	Normal
22	Follow Up	Cyclosporine	S.K	7	M	28-09-2014	13.7	81	20.9	Normal
23	Follow Up	Cyclosporine	R.P	3.8	M	11-01-2018	13	100	13	Obese
24	Follow Up	Cyclosporine	D.K	5	F	22-01-2016	17.3	104	16	Underweight
25	Follow Up	Cyclosporine	P.S	7	M	05-02-2014	18	112	14.3	Normal
26	New	Tacrolimus	L.S	6	M	01-03-2016	16.9	109	14.2	Normal
27	New	Tacrolimus	K.K	5	M	17-08-2017	13	90	16	Normal
28	New	Tacrolimus	S.K	10	F	07-11-2012	23	126	14.5	Underweight
29	New	Tacrolimus	B.S	7	M	21-11-2014	22.5	113	17.2	Overweight
30	New	Tacrolimus	A.K	14	F	07-09-2008	46.5	155	19.4	Normal
31	New	Tacrolimus	A.K	1.2	M	03-03-2021	10.5	80	16.4	Normal
32	New	Tacrolimus	A.L	5.6	F	20-09-2016	21.4	103	20.2	Obese
33	New	Tacrolimus	C.V	9.5	M	01-04-2012	23	102	22.1	Obese
34	New	Tacrolimus	A.K	13	F	07-09-2009	42	152	18.2	Normal
35	New	Tacrolimus	M.A	13.3	M	19-09-2008	47	158	18.8	Normal

Sl. No.	Age Of Onset(Year / Month)	Urban/Rural	File No. (Ped. Nephro)	Steroid Resistant (Early/ Late)	Hypertension at onset (Y/N)	Genetic Testing	Family history / Any Sibling Effected
1	2.9	URBAN	392	EARLY	N	NOT DONE	NO
2	2	URBAN	416	EARLY	N	NOT DONE	NO
3	6	RURAL	516	EARLY	Y	NOT DONE	NO
4	2.7	RURAL	531	EARLY	N	NOT DONE	NO
5	5	URBAN	508	EARLY	N	NOT DONE	NO
6	4.5	URBAN	523	EARLY	N	NOT DONE	NO
7	5	URBAN	438	EARLY	N	NOT DONE	NO
8	0.9	URBAN	596	EARLY	N	NOT DONE	NO
9	5.6	RURAL	450	EARLY	N	NOT DONE	NO
10	4	RURAL	411	EARLY	Y	NOT DONE	NO
11	4	URBAN	522	EARLY	N	NOT DONE	NO
12	4	URBAN	521	EARLY	N	NOT DONE	NO
13	4	RURAL	519	EARLY	N	NOT DONE	NO
14	3	RURAL	464	EARLY	N	NOT DONE	NO
15	3	URBAN	600	EARLY	N	NOT DONE	NO
16	4	URBAN	336	EARLY	Y	NOT DONE	NO
17	3	URBAN	152	EARLY	N	NOT DONE	NO
18	2	URBAN	549	EARLY	N	NOT DONE	NO
19	2.8	URBAN	366	EARLY	N	NOT DONE	NO
20	2.6	URBAN	20	EARLY	N	NOT DONE	NO
21	1.2	RURAL	245	EARLY	N	NOT DONE	NO
22	1.5	URBAN	345	EARLY	N	NOT DONE	NO
23	1.5	URBAN	470	LATE	N	NOT DONE	NO
24	3	URBAN	440	LATE	Y	NOT DONE	NO
25	3	URBAN	357	EARLY	N	NOT DONE	NO
26	6	URBAN	598	EARLY	N	NOT DONE	NO
27	4.5	URBAN	541	EARLY	N	NOT DONE	NO
28	10	URBAN	602	EARLY	N	NOT DONE	NO
29	2	URBAN	563	EARLY	N	NOT DONE	NO
30	3.5	RURAL	611	EARLY	N	NOT DONE	NO
31	1	URBAN	623	EARLY	N	NOT DONE	NO
32	5	URBAN	599	EARLY	N	NOT DONE	NO
33	5	URBAN	621	EARLY	N	NOT DONE	NO
34	3.5	URBAN	643	LATE	N	NOT DONE	NO
35	12	URBAN	584	LATE	N	NOT DONE	NO

Sl. No.	Haematuria at onset (Y/N)	Cataract	Cushingoid	Hypertension	Short Stature	Renal Biopsy Findings	Hemoglobin	Total Leucocyte Count	PLATELETS	UREA	CREATININE	SODIUM
1	N	NO	YES	NO	NO	NOT DONE	12.9	32200	5.6	28	0.37	138
2	N	NO	NO	NO	NO	FSGS (TIP)	12.1	12900	4.6	36	0.4	133
3	N	NO	NO	NO	NO	NOT DONE	13.6	23200	4.2	21	0.43	131
4	N	NO	YES	NO	NO	NOT DONE	12.1	13500	4.92	43	0.25	133
5	Y	NO	YES	NO	NO	FSGS (NOS)	13.9	7200	3.6	25	0.5	135
6	N	NO	YES	NO	NO	NOT DONE	13.1	19500	2.4	29	0.15	143
7	N	NO	YES	YES	NO	NOT DONE	13.6	23380	3.1	20	0.6	143
8	N	NO	YES	YES	NO	MCD	12.8	13500	2.8	18	0.42	133
9	N	NO	YES	YES	NO	NOT DONE	11.3	17800	3.5	19	0.5	135
10	N	NO	YES	YES	NO	ADVANCED GLOMERULOSCLEROSIS	9.2	14200	2.6	18	0.1	130
11	N	NO	YES	YES	NO	FSGS (TIP)	12.3	17400	5.2	26	0.2	141
12	Y	NO	NO	YES	NO	MPGN	9.68	10700	1.16	18	0.7	137
13	N	NO	YES	NO	NO	NOT DONE	12.4	11000	2.4	96	0.55	138
14	N	NO	YES	NO	NO	FSGS (TIP)	13.1	14300	2.16	21	0.19	143
15	N	NO	NO	NO	NO	NOT DONE	13.2	10000	2.4	18	0.21	145
16	N	NO	YES	YES	NO	NOT DONE	10.8	14000	2.84	16	0.33	136
17	N	NO	YES	NO	NO	FSGS (NOS)	10.9	18900	3.1	31	0.8	148
18	N	NO	NO	NO	NO	NOT DONE	13.8	13000	3.12	12	0.3	143
19	N	NO	YES	YES	NO	NOT DONE	13.5	12500	3.2	63	0.21	140
20	N	NO	YES	NO	NO	MCD	13.9	18600	3.4	19	0.5	138
21	N	NO	YES	NO	NO	MCD	6.5	14800	5.7	15	0.16	137
22	N	NO	YES	NO	NO	FSGS (TIP)	13	12300	5.1	9	0.15	140
23	N	NO	YES	YES	NO	NOT DONE	9.4	4700	3.4	44	0.42	143
24	N	NO	YES	YES	NO	NOT DONE	12	10200	4.49	39	0.3	137
25	N	NO	YES	NO	NO	MCD	10	12000	3.4	72	0.38	133
26	N	NO	YES	NO	NO	MEMBRANOUS NEPHROPATHY	9.6	9100	6.3	46	0.4	136
27	N	NO	YES	NO	NO	NOT DONE	12.6	11550	3.89	10	0.17	140
28	N	NO	YES	NO	NO	MCD	14.8	14400	2.8	29	0.8	140
29	N	NO	YES	YES	NO	FSGS (TIP)	14.2	13000	4.2	21	0.18	133
30	N	NO	YES	NO	NO	FSGS (TIP)	13.2	13400	3.84	26	0.39	143
31	N	NO	NO	NO	NO	NOT DONE	12.8	12000	3.1	17	0.4	136
32	N	NO	YES	NO	NO	NOT DONE	12.1	11000	3.1		0.18	
33	N	NO	YES	NO	NO	FSGS (TIP)	13	10600	5.7		0.12	
34	N	NO	YES	NO	NO	FSGS (TIP)	11.8	12300	3.4	18	0.6	132
35	N	NO	YES	NO	NO	NOT DONE	12.5	12240	3.7	15	0.42	133

Sl. No.	POTASSIUM	VIRAL MARKERS	SERUM ALBUMIN	SERUM GLUCOSE	FT3	FT4	THYROID STIMULATING HORMONE	CHOLESTEROL	TRIGLYCERIDE	HIGH DENSITY LIPOPROTEIN
1	5.13	NR	2.48	98	1	6.8	11	484	318	3.2
2	4.72	NR	3.1	88			14.99	610	515	27
3	5.18	NR	1.95	104	4	20	2.4	398	210	50
4	5.38	NR	1.72	105	1.5	5.9	12	250	190	60
5	3.9	NR	2	102	1.2	7.2	15	400	280	40
6	4.3	NR	1.86	96	3.5	18	2.5	101	156	34
7	4.48	NR	2.09	84			12	427	342	86
8	4.4	NR	2.48	96			2.9	244	185	34
9	4.4	NR	1.84	94			10.53	568	441	38
10	4.4	NR	2.1	104	3.6	14.4	4.4	651	586	89
11	5.01	NR	2.48	92	4.1	13.4	3.88	263	184	33
12	4	NR	2.5	92	4.4	12.8	4.2	195	108	31
13	3.19	NR	2.12	58	5	13	3.5	240	184	40
14	4.2	NR	3.2	94	3.99	14.54	4.76	344	216	25
15	4.4	NR	2.49	89	3.6	12.2	11.6	189	110	40
16	4.4	NR	2.9	96	4.3	13	4.1	276	187	38
17	4.3	NR	2.15	100	3.5	13.4	3.6	248	118	40
18	4.3	NR	2.7	99	4.1	13.4	3.5	344	216	64
19	4.17	NR	2.4	104	6	11	13	413	240	38
20	4.5	NR	2	95			2.35	302	213	26
21	4.6	NR	2.6	95	3.1	15	3.6	398	222	70
22	4.25	NR	1.97	106	6	12	2.5	284	170	25
23	4.4	NR	2.24	96	3.8	11.6	4.4	440	322	30
24	4.68	NR	1.99	107	4.1	12.2	3.99	157	101	18
25	4.2	NR	1.86	92	4.6	11.5	3.88	450	340	59.4
26	5.4	NR	2.74	98	4.5	15	4.22	398	244	30
27	4.33	N.R	2.78	82	4.8	14.63	5.92	265	156	28
28	5.35	N.R	2.16	98	4.4	13.1	4.32	436	318	44
29	4.2	NR	2.2	90	3.8	11.2	13.43	292	184	35
30	4.65	NR	2.7	92	4.1	11.4	2.6	248	118	42
31	4.1	NR	2.5	86			2.9	243	133	32
32		NR	2.84				3.1	188	211	38
33		NR	2.93				3.45	198	146	39
34	3.89	NR	3.2	87	4.1	11.6	3.9	184	137	34
35	4.6	NR	3.4	76	4.4	12.1	3.76	223	158	32

Sl. No.	LOW DENSITY LIPOPROTEIN	CALCIUM	PHOSPHORUS	ALKALINE PHOSPHATASE	URINE ROUTINE			SPOT URINARY PROTEIN CREATININE RATIO	24 HOUR URINARY PROTEIN
					ALBUMIN	PUS CELL	RED BLOOD CELLS		
1	50.4	7.8	4.2	60	2+	810	NIL	3.12	
2	56.3	7.7	3.8	74	2+	NIL	5-10	3.1	
3	28	8.2	3.8	68	4+	2	1	13.9	
4	38	8.1	3.6	72	3+	NIL	NIL	21.7	
5	80	8	4.1	68	3+	8-10	NIL	9.03	
6	43	7.3	5	70	3+	NIL	OCCASSIONAL	10.1	
7	321				3+	NIL	NIL	9.9	
8	64	8.1			3+	NIL	NIL	6.1	
9	101	8.2			3+	NIL	NIL	8.4	
10	432	7.5	5.2	74	3+	2-4	OCCASSIONAL	5.4	
11	54	9.5		59	3+	NIL	4-6	8.4	
12	40				4+	8-10	10-15	4.2	
13	80	7.1			3+	NIL	NIL	8.4	
14	48	8.1			3+	NIL	NIL	8.4	
15	54	7.6			3+	NIL	NIL	4.88	
16	49	7.5			3+	NIL	NIL	6.4	
17	67	8.1			3+	NIL	10-15	5.4	
18	38	7.9			3+	NIL	NIL	8.5	
19	64	8.1			4+	NIL	NIL	9.3	
20	34				3+	10-12	NIL	4.4	4.4
21	282	8.4	4	70	3+	2-4	NIL	4.48	
22	41	8.46			3+	NIL	1-2	6.44	
23	84				3+	NIL	NIL	8.24	
24	24				3+	NIL	NIL	8.4	
25	24.8				3+	NIL	1-2	7.3	7380 mg
26	56	9.4			3+	NIL	4-5	7.4	
27	43	8.1			3+	NIL	NIL	6.92	228.5
28	49	7.8			3+	NIL	NIL	13.8	
29	53	8.1			3+	NIL	4-6	5.84	
30	60				3+	NIL	4-8	7.24	
31	46	7.6			3+	5-6	NIL	4.2	
32	51				3+	NIL	NIL	3.42	
33	44				3+	NIL	NIL	4.22	
34	37	7.8			3+	NIL	NIL	4.89	
35	41	8.1			3+	NIL	NIL	4.2	

Sl. No.	ULTRASOUND ABDOMEN	CHEST XRAY	Date Of Start Of Tacrolimus/ Cyclosporine	Age At Start Of Tacrolimus/Cyclosporine	Dose Given (Mg/Kg)
1	WNL	WNL	26-02-2018	3.1	0.07
2	WNL	WNL	17-10-2018	2.3	0.08
3	WNL	WNL	29-06-2020	6. 10	0.1
4	WNL	WNL	10-11-2020	3	0.1
5	WNL	WNL	18-08-2020	10.4	0.1
6	MILD ASCITES	WNL	26-06-2020	5	0.06
7	WNL	WNL	08-02-2019	5.3	0.12
8	MILD PLEURAL EFFUSION	EFFUSION	28-10-2015	5	0.13
9	Mild to mod ascites, reactive gall bladder edema	WNL	15-04-2019	5.8	0.1
10	WNL	WNL	27-07-2018	4.1	0.05
11	WNL	WNL	15-05-2020	4.3	0.06
12	WNL	WNL	01-03-2019	5.2	0.1
13	WNL	WNL	04-05-2020	4.5	0.1
14	MILD ASCITES	WNL	MARCH, 2018	9	0.1
15	WNL	WNL	07-11-2019	4.1	0.1
16	WNL	WNL	20-06-2020	5.6	0.1
17	WNL	WNL	19-01-2015	3.7	0.1
18	MILD ASCITES	WNL	02-04-2021	2.7	0.1
19	WNL	WNL	15-11-2017	3.1	0.1
20	WNL	BILATERAL INFILTRATES	29-06-2009	2.9	4
21	WNL	WNL	01-09-2014	1.83	4
22	B/L KIDNEY LOBULATED, CORTICAL ECHOGENECITY INCREASED	WNL	28-08-2017	2.11	4
23	WNL	WNL	15-02-2021	3.1	4
24	WNL	WNL	24-07-2020	4.6	4
25	WNL	WNL	13-09-2017	3.7	4
26	MINIMAL ASCITES, MODERATE LEFT PLEURAL EFFUSION	PLEURAL EFFUSION	13-05-2022	6.2	0.1
27	WNL	WNL	FEB,2022	4.6	0.1
28	MILD ASCITES	WNL	28-05-2022	10	0.1
29	MILD ASCITES	MILD PLEURAL EFFUSION	27-08-2021	7	0.1
30	MILD ASCITES	WNL	27-04-2022	14	0.1
31	WNL	WNL	17-05-2022	1.2	0.1
32	WNL	WNL	02-02-2022	5.5	0.1
33	WNL	WNL	02-08-2021	9.4	0.1
34	WNL	WNL	23-03-2022	12.6	0.1
35	WNL	WNL	21-12-2021	13.3	0.1

Sl. No.	Associated Medications	Side effects of Tacrolimus/Cyclosporine: (Yes/No)	Hypertension	Hyperkalemia	Seizure	Increase Blood Sugar	Increase OT/ PT	Diarrhea	UTI
1	ENVAS		N	N	N	N	N	N	N
2	ENVAS		N	N	N	N	N	N	N
3	ENVAS		N	N	N	N	N	N	N
4	ENVAS		N	N	N	N	N	N	N
5	CARDACE		Y	N	N	N	N	N	N
6	ENVAS		Y	N	N	N	N	Y	N
7	ENVAS		Y	N	N	N	N	N	N
8	ENVAS		Y	N	N	N	N	Y	N
9	ENVAS, ISONIAZID		Y	N	N	N	N	N	Y
10	ENVAS		Y	N	N	N	N	N	Y
11	ENVAS		Y	N	N	N	N	N	Y
12	ENVAS		Y	N	N	N	N	N	N
13	-		N	N	N	N	N	N	N
14	-		N	N	N	N	N	N	N
15	ENVAS		Y	N	N	N	N	N	N
16	ENVAS		Y	N	N	N	N	N	N
17	LOSARTAN		Y	N	N	N	N	N	N
18	ENVAS		Y	N	N	N	N	N	N
19	ENVAS		N	N	N	N	N	N	N
20	ENVAS		Y	N	N	N	N	N	Y
21	ENVAS		N	N	N	N	N	N	N
22	ENVAS		N	N	N	N	N	Y	N
23	ENVAS		N	N	N	N	N	N	N
24	ENVAS		Y	N	N	N	N	N	Y
25	ENVAS		Y	N	N	N	N	N	N
26	-		N	N	N	N	N	N	N
27	ENVAS		N	N	N	N	N	N	N
28	ENVAS		N	N	N	N	N	N	N
29	ENVAS		Y	N	N	N	N	N	N
30	ENVAS		N	N	N	N	N	N	N
31	ENVAS		N	N	N	N	N	N	N
32	ENVAS		N	N	N	N	N	N	N
33	-		N	N	N	N	N	N	N
34	-		N	N	N	N	N	N	N
35	-		N	N	N	N	N	N	N

Sl. No.	Reversible Nephropathy	Hypertrichosis	Gingival Hyperplasia	Acne	Skin infections	Major infection (Requiring hospitalization)Diagnosis	Others
1	N	N	N	N	N	N	N
2	N	N	N	N	N	N	N
3	N	N	N	N	N	N	N
4	N	N	N	N	N	N	N
5	N	N	N	N	N	N	N
6	N	N	N	N	N	N	N
7	N	N	N	N	N	N	N
8	N	N	N	N	N	YES, PNEUMONIA	N
9	N	N	N	N	N	PNEUMONIA, BRONCHIOLITIS	N
10	N	N	N	N	N	N	N
11	N	N	N	N	N	N	N
12	N	N	N	N	N	URI	N
13	N	N	N	N	N	N	N
14	N	N	N	N	N	N	N
15	N	N	N	N	N	N	N
16	N	N	N	N	N	N	N
17	N	N	N	N	N	N	N
18	N	N	N	N	N	N	ORAL THRUSH
19	N	N	N	N	N	N	N
20	N	N	N	N	N	UTI	H/O PULMONARY KOCH
21	N	N	Y	N	N	N	URI
22	N	N	N	N	N	YES, PNEUMONIA	URI
23	N	N	N	N	N	N	N
24	N	N	N	N	N	N	LRTI
25	N	N	N	N	N	N	N
26	N	N	N	N	N	YES, PRESS	N
27	N	N	N	N	N	N	N
28	N	N	N	N	N	N	N
29	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N
31	N	N	N	N	N	N	N
32	N	N	N	N	N	N	N
33	N	N	N	N	N	N	N
34	N	N	N	N	N	N	N
35	N	N	N	N	N	N	N

Sl. No.	Paramenters Monitoring Details	URINE ALBUMIN 1	URINE PROTEIN CREATININE RATIO	24 HR URINE PROTEIN 1	SERUM ALBUMIN 1	SERUM CREATININE 1	ELECTROLYTES (SODIUM) 1	ELECTROLYTES (POTASSIUM) 1	Drug Levels LEVELS 1	EDEMA 1	URINE ALBUMIN 3	URINE PROTEIN CREATININE RATIO
1		NIL	0.17		3.1	0.4	138	4.1		NO	NIL	0.11
2		NIL	0.19		3.2	0.1	133	4.83	1.8	NO	1+	0.68
3		3+	3.84		2.67	0.35	138	3.44		YES	1+	0.62
4		3+	15		2.17	0.22	139	4.2	2.1	YES	3+	9.9
5		3+	8.1		1.99	0.3	137	4.25	3.5	YES	3+	6.8
6		1+	1.4		3.56	0.28	144	3.9		NO	TRACE	0.19
7		1+	0.88		3.55	0.45	138	4		YES	NIL	0.18
8		2+	1.8		2.54	0.6	136	4.2		YES	NIL	0.15
9		3+	3.6		2.2	0.18	136	4.2		YES	2+	1.8
10		2+	1.68		1.9	0.4	133	5.1		YES	2+	1.87
11		NIL	0.18		3.5	0.2	140	4.3		NO	NIL	0.18
12		1+	1.56		2.2	0.9	133	4.2		YES	NIL	0.16
13		2+	1.88		2.01	0.19	136	4	2	YES	2+	1.92
14		TRACE	0.18		2.9	0.4	137	4.2		NO	NIL	0.11
15		NIL	0.17		3.1	0.12	135	4.4	1.7	NO	NIL	0.19
16		2+	1.98		2.6	0.22	134	4.7		YES	TRACE	0.19
17		3+	4.4		2.7	0.16	133	4.5		YES	3+	4.13
18		2+	2.1		2.7	0.14	136	4.2	4.1	YES	3+	3.22
19		3+	4.3		2.1	0.2	137	4.2	10	YES	2+	1.88
20		NIL	0.16		3.1	0.4	133	4.5		NO	NIL	0.17
21		NIL	0.16		2.9	0.4	136	4.2		NO	NIL	0.15
22		2+	1.98		2.4	0.33	141	3.25		YES	2+	1.79
23		NIL	0.12		3.4	0.32	142	3.8		NO	NIL	0.12
24		3+	3.87		2.1	0.4	137	4.2		YES	4+	4.59
25		+	0.98		3.1	0.63	136	4.4		YES	NIL	0.34
26		2+	1.9		2.4	0.5	136	4.2		YES	1+	0.94
27		NIL	0.14		3.1	0.14	138	4.2		NO	NIL	0.16
28		TRACE	0.19		3.4	0.36	141	3.9	1.7	NO	NIL	0.11
29		2+	1.8		2.8	0.6	138	4.2	1.59	YES	1+	0.9
30		3+	4.4		2.21	0.39	143	4.6		YES	3+	3.87
31		NIL	0.14		2.99	0.14	144	3.8	11.6	NO	NIL	0.15
32		NIL	0.14		3.22	0.16	138	4.1		NO	NIL	0.16
33		NIL	0.18		3.43	0.11				NO	NIL	0.1
34		3+	3.78		2.8	0.43	137	4.4	5.99	YES	3+	3.89
35		3+	4.1		2.9	0.42	137	4.21		YES	3+	3.88

Sl. No.	24 HR URINE PROTEIN 3	SERUM ALBUMIN 3	SERUM CREATININE 3	ELECTROLYTES (SODIUM) 3	ELECTROLYTES (POTASSIUM) 3	Drug Levels LEVELS 3	EDEMA 3	URINE ALBUMIN 6	URINE PROTEIN CREATININE RATIO	24 HR URINE PROTEIN 6	SERUM ALBUMIN 6	SERUM CREATININE 6	ELECTROLYTES (SODIUM) 6
1		3.4	0.38	144	4.2	2.09	NO	NIL	0.16		3.23	0.22	133
2		3.1	0.43	136	4.22	1.67	NO	NIL	0.11		3.41	0.42	138
3		3.12	0.29	139	4.22		NO	NIL	0.17		3.8	0.19	139
4		2.63	0.15	135	3.8	4.47	YES	3+	4.4		2.9	0.3	134
5		2.24	0.4	139	4.2		YES	3+	3.9		2.98	0.1	138
6		3.8	0.31	139	4.76	1.8	NO	TRACE	0.16		3.81	0.2	143
7		3.99	0.38	133	3.7		NO	NIL	0.12		3.89	0.33	139
8		3.1	0.42	137	3.9	6.13	NO	TRACE	0.19		3.25	0.39	142
9		2.9	0.29	141	3.9		YES	1+	1.88		2.9	0.43	133
10		1.8	0.2	131	4.1	6.42	YES	2+	1.59		2.76	0.3	126
11		3.62	0.3	140	4.7	2.1	NO	TRACE	0.23		3.22	0.18	139
12		3.1	0.3	136	4.4		NO	NIL	0.11		3.4	0.45	138
13		2.48	0.22	137	4.5		YES	2+	1.67		2.92	0.34	130
14		3.2	0.3	136	4.1	4.3	NO	NIL	0.19		3.3	0.4	139
15		3.3	0.16	137	3.6	1.8	NO	NIL	0.11		3.1	0.22	139
16		3.1	0.31	139	4.1		NO	TRACE	0.17		3.16	0.26	143
17		2.9	0.23	137	4.2	4.11	YES	3+	3.99		2.4	0.31	139
18		2.9	0.23	139	4.1	2.2	YES	TRACE	0.19		3.2	0.19	141
19		3.1	0.31	141	3.8		YES	2+	1.9		2.7	0.16	139
20		3.2	0.31	136	4.8		NO	NIL	0.11		2.01	0.36	139
21		2.71	0.38	137	4.8	178	NO	NIL	0.17		3.1	0.24	141
22		2.6	0.41	133	4.4		YES	2+	1.84		2.92	0.29	137
23		3.4	0.32	142	3.8		NO	NIL	0.16		3.42	0.37	137
24		2.23	0.31	142	4.7		YES	3+	3.12		2.99	0.18	134
25		2.9	0.48	139	4.2		NO	NIL	0.16		3.4	0.5	143
26		2.84	0.4	137	4.4	2.86	NO	TRACE	0.16		3.01	0.32	139
27		3.2	0.19	137	4.1		NO	NIL	0.18		3.36	0.25	133
28		3.8	0.4	143	3.4	3.56	NO	TRACE	0.19		2.99	0.48	139
29		3.12	0.4	142	5.1	3.58	NO	TRACE	0.19		3.31	0.29	144
30		2.22	0.43	143	5.1	5.86	YES	2+	1.89		2.85	0.34	142
31		3.3	0.15	133	4.6	6.07	NO	NIL	0.17		3.42	0.18	143
32		3.8	0.18				NO	NIL	0.19		4	0.23	133
33		3.41	0.16				NO	NIL	0.18		3.62	0.19	
34		2.89	0.43	138	5.1	5.78	YES	2+	2		2.9	0.32	137
35		2.9	0.41	142	5	6.01	YES	2+	2		3.1	0.43	143

Sl. No.	ELECTROLYTES (POTASSIUM) 6	Drug Levels LEVELS 6	EDEMA 6	ANY OTHER SIDE	STATUS OF PATIENTS AT 3 MONTHS : CR/PR/NR	STATUS OF PATIENTS AT 6 MONTHS : CR/PR/NR	Drug Given For Duration (Months)	Off Steroids (Y/N)
1	3.7	3.72	NO	N	CR	CR	34	NO
2	3.83	2.82	NO	N	PR	CR	30	NO
3	4.11	2.14	NO	N	PR	CR	21	NO
4	5.11	3.16	YES	N	NR	NR	18	NO
5	6.04	4.2	YES	N	NR	NR	18	NO
6	4.1	2.4	NO	N	CR	CR	24	YES
7	4.1	4.42	NO	N	CR	CR	35	NO
8	4.2		NO	N	CR	CR	39	NO
9	4.8		NO	N	PR	PR	30	NO
10	4		NO	N	PR	PR	37	NO
11	4.7	5.08	NO	N	CR	CR	24	NO
12	4.4		NO	N	CR	CR	30	NO
13	4.2		NO	N	PR	PR	18	NO
14	4.4	5.15	NO	N	CR	CR	36	YES
15	4.1	3.2	NO	N	CR	CR	28	NO
16	3.5	1.52	NO	N	CR	CR	24	NO
17	3.6	3.26	YES	N	NR	NR	38	NO
18	3.7	4.9	NO	N	NR	CR	13	NO
19	3.2	4.8	NO	N	PR	PR	36	NO
20	4.1		NO	N	CR	CR	27	NO
21	3.9	456	NO	N	CR	CR	40	NO
22	4.6		NO	N	PR	PR	38	NO
23	4.6		NO	N	CR	CR	11	YES
24	4.5		YES	N	NR	NR	18	YES
25	4.2		NO	N	CR	CR	35	NO
26	4.1	3.33	NO	N	PR	CR	6	NO
27	5.1		NO	UTI	CR	CR	6	NO
28	3.8	3.67	NO	N	CR	CR	6	NO
29	5.3	2.38	NO	N	PR	CR	6	YES
30	4.8	4.9	NO	N	NR	PR	6	NO
31	4.2		NO	N	CR	CR	6	NO
32	4.2	7.14	NO	N	CR	CR	6	NO
33			NO	N	CR	CR	6	NO
34	4.68	4.97	NO	N	NR	PR	6	NO
35	4.65	7.54	NO	N	NR	PR	6	NO

Sl. No.	If Yes, Duration Off Steroids	Change of Therapy	Relapse	Remission (Month)	No. Of Relapses After Starting Drug (In 12 Months Peroid)	Drug Started (Rituximab)/Cyclophosphamide (Y/N)
1	NO	NO	NO	1ST	NO	NO
2	NO	NO	NO	1ST	NO	NO
3	NO	NO	NO	3RD	NO	NO
4	NO	NO	YES	8TH	2	NO
5	NO	YES	YES	11TH	3	YES (Cyclophosphamide)
6	10	NO	NO	1ST	NO	NO
7	NO	NO	NO	1ST	NO	NO
8	NO	NO	NO	1ST	NO	NO
9	NO	NO	YES	3RD	1	NO
10	NO	YES	YES	1ST	3	YES(RITUXIMAB)
11	NO	NO	YES	1ST	1	NO
12	NO	NO	YES	1ST	2	NO
13	NO	NO	NO	1ST	NO	NO
14	24 MONTHS	NO	NO	1ST	NO	NO
15	NO	NO	NO	1ST	NO	NO
16	NO	NO	YES	3RD	2	NO
17	NO	NO	YES	11TH	1	NO
18	NO	NO	YES	1ST	1	NO
19	NO	YES	YES	3RD	2	YES (RITUXIMAB)
20	NO	NO	YES	1ST	1	NO
21	NO	NO	YES	1ST	1	NO
22	NO	NO	NO	1ST	NO	NO
23	7 MONTHS	NO	NO	1ST	NO	NO
24	7 MONTHS	NO	YES	9TH	1	NO
25	NO	NO	NO	1ST	NO	NO
26	NO	NO	NO	1ST	NO	NO
27	NO	NO	NO	1ST	NO	NO
28	NO	NO	NO	1ST	NO	NO
29	4	NO	NO	1ST	NO	NO
30	NO	NO	NO	6TH	NO	NO
31	NO	NO	NO	1ST	NO	NO
32	NO	NO	NO	1ST	NO	NO
33	NO	NO	NO	1ST	NO	NO
34	NO	NO	NO	6TH	NO	NO
35	NO	NO	NO	6TH	NO	NO

Sl. No.	Response At 6 Months Post Rituximab/Cyclophosphamide (CR/PR/NR	Status of patient at last follow up
1	NO	CR
2	NO	CR
3	NO	PR
4	NO	PR
5	CR	CR
6	NO	CR
7	NO	CR
8	NO	CR
9	NO	PR
10	PR	PR
11	NO	CR
12	NO	CR
13	NO	CR
14	NO	CR
15	NO	CR
16	NO	CR
17	NO	PR
18	NO	NR
19	CR	CR
20	NO	CR
21	NO	CR
22	NO	CR
23	NO	CR
24	NO	NR
25	NO	CR
26	NO	CR
27	NO	CR
28	NO	CR
29	NO	CR
30	NO	PR
31	NO	CR
32	NO	CR
33	NO	CR
34	NO	PR
35	NO	PR

Baba Farid University
of Health Sciences
Sadiq Road
Faridkot-151 203 (Pb). INDIA.
Phone : 01639-256232,256236
Tele/Fax : 01639-256235
Email - Examination@bfuhs.ac.in

No. BFUHS/2K21p-TH/ 2-2 Date 6/1/22

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.10.2021 has approved the plan of thesis of **Tanish Dhir**, a student of your college for **DM Nephrology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Clinical profile, treatment practices and outcome in children with steroid resistant nephrotic syndrome.

Supervisor
Dr. Preet Mohinder Singh
Assoc. Prof.,
Dept. of Nephrology,
DMCH, Ludhiana.

Co-Supervisor

Dr. Gurdeep Singh Dhooria
Prof.,
Dept. of Paediatrics,
DMCH, Ludhiana.

Dr. Suman Sethi
Asst. Prof.,
Dept. of Nephrology,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

SPS
Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

169. If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.

170. The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.

CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOMES IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED
IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

D.M

in

NEPHROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

AUGUST, 2021

DR. TANISH DHIR

DEPARTMENT OF NEPHROLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL,
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	**CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOMES IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME**
For the degree of	D.M Nephrology
Name of the candidate	Dr. Tanish Dhir
Supervisor	Dr. Preet Mohinder Singh, Associate Professor, Department of Nephrology, DMCH, Ludhiana
Co-supervisor	Dr. Gurdeep Singh Dhooria, Professor, Department of Paediatrics, DMCH, Ludhiana Dr. Suman Sethi, Assistant Professor, Department of Nephrology, DMC & Hospital, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Nephrotic syndrome is the most frequently occurring glomerular disease in the childhood .Steroid resistant Nephrotic Syndrome (SRNS) is defined as absence of complete remission of proteinuria despite 4 weeks of therapy with full dose prednisone .Management of these SRNS patients are challenging .Treatment options are limited with use of CNI's being one of the most commonly used therapy. There are no studies on clinical profile and management options in SRNS in our region. Hence, need of this study is required.

Aim of Study: 1) Clinical profile of children with steroid resistant nephrotic syndrome (SRNS) 2) Treatment practices and outcomes in these SRNS children.

Materials & Methods: It will be an observational hospital-based study of patients from August, 2021 to May, 2022 of SRNS who will be newly diagnosed along with patients who are already known case of SRNS and are on immunosuppression with follow up of at least 6 months.

Clinical Significance: Steroid Resistant Nephrotic syndrome which accounts for 10-15% cases, are difficult to manage. Treatment options are limited with less favourable outcomes. This study will evaluate the outcomes and may help in better safety profile and management.

Keywords: Nephrotic Syndrome, Steroid Resistant Nephrotic Syndrome, Calcineurin Inhibitors

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Supervisor	Co-Supervisor	Co-Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOMES IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME"** exist in the Department of Nephrology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

Supervisor

Dr. Preet Mohinder Singh
Associate Professor
Department of Nephrology
DMCH, Ludhiana

Co-Supervisors

Dr. Gurdeep Singh Dhooria
Professor
Department of Paediatrics
DMCH, Ludhiana

Dr. Suman Sethi
Assistant Professor
Department of Nephrology
DMC & Hospital, Ludhiana

Head of the Department

Dr. Vikas Makkar
Professor & Head
Department of Nephrology
DMCH, Ludhiana

Place: LUDHIANA

Date: 26/8/21

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Tanish Dhir
Department	Nephrology
Topic of Thesis	CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOMES IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME
Likely date of appearing in PG examination	May/June 2023
Date of enrollment	29/12/2020
Name of Head of Department	Dr. Vikas Makkar
1. Supervisor **2. Co-Supervisor**	Dr. Preet Mohinder Singh Dr. Gurdeep Singh Dhooria Dr. Suman Sethi
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Harpreet Kaur (Professor & Head, Pathology)	Mr. R K Sharma (Legal Expert)
Dr. Jaspal Singh (Professor & Head, Surgery)	Dr. Ramit Mahajan (Associate Professor, Gastroenterology)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)	Dr. Sandeep Kaushal (Dean Academics & Professor & Head, Pharmacology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal & Professor & Head, Cardiology)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / No

Dr. Sandeep Puri
Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
Chairperson
Ethics Committee

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Tanish Dhir Dhir Hospital, Outside Zira Gate, Ferozepur City, Punjab
2	NAME OF THE INSTITUTE	Dayanand Medical College & Hospital, Ludhiana
3	COURSE OF STUDY AND SUBJECT	D.M in Nephrology
4	DATE OF ADMISSION OF COURSE	29/12/2020
5	TITLE OF THE TOPIC	Clinical Profile, treatment practices and outcomes in children with Steroid Resistant Nephrotic Syndrome

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Nephrotic syndrome is the most frequently occurring glomerular disease in the childhood. It usually begins between the age of 2 - 5 years with the diagnosis of nephrotic syndrome requiring the presence of Nephrotic range proteinuria: >=3 + by dipstick, proteinuria >40mg/m^2/hr (>1000mg/m^2/day), urine protein to creatinine ratio (Up/Uc) >=2mg/mg; hypoalbuminemia (< 3g/dl) and edema [1]. Idiopathic nephrotic syndrome (INS) represents more than 90% of cases between 1 - 10 years of age and 50 % beyond 10 years of age [2]. The prevalence of Idiopathic Nephrotic syndrome varies from 12-16 per 100000 children [3].

Majority of children are with Minimal Change Disease with more than 90% of children responding to long term steroid therapy while only 50% of mesangial proliferation and 30% of focal segmental glomerulosclerosis responds to steroid therapy [4]. Majority of the children achieve remission in 4 weeks. Some children have no response to steroid and are considered as Steroid Resistant Nephrotic syndrome (SRNS) while there are some children that relapse after lowering the dose or stopping the steroid and are considered as Steroid Dependent Nephrotic Syndrome (SDNS). The management of steroid-resistant nephrotic syndrome, which accounts for 10%–15% of nephrotic syndrome in children, is a herculean task [5]. SRNS is defined as absence of complete remission of proteinuria despite 4 weeks of therapy with full dose prednisone (2 mg/kg/day or 60mg/m^2/day) either at disease onset (initial, primary) or following a subsequent relapse (late, secondary). All SRNS patients should undergo a kidney biopsy to determine the histopathological pattern. Renal histology shows Focal segmental glomerulosclerosis (FSGS), Minimal change disease (MCD), Mesangioproliferative Glomerulonephritis (MesGN). Other patterns, including C3 Glomerulopathy, Membranous Nephropathy and IgA nephropathy, and secondary causes of nephrotic syndrome are uncommon. The management of these SRNS patients are challenging

with unsatisfactory quality of life, morbidity due to infectious and non-infectious illnesses and side effects of intensified immunosuppression [5,6]. With the difference in pathogenesis, treatment response, and outcomes, individualization of the cause and subsequent therapy is needed. Immunosuppressant drugs such as Cyclophosphamide and Cyclosporine-A have been used in patients who have no response to steroid but the treatment options like Cyclosporine-A have high relapse and resistant rate[7]. Other treatment options include CNIs (Calcineurin inhibitors) like tacrolimus which can be used and have a documented better safety profile with a higher remission and a lower relapse rate [8]. Tacrolimus and prednisolone are effective, safe, and preferable to cyclophosphamide as the initial therapy for patients with steroid-resistant nephrotic syndrome[9,10]. Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome has also been documented [11]. In patients with non-genetic form of SRNS (25-35%) who do not show complete or partial remission and are non-responsive to therapy with CNI, Rituximab has been tried but its efficacy is less satisfactory with complete or partial remission observed in 46.4% with better response in MCD (63.2%) than in FSGS (39.2%) and late (52.8%) compared to initial resistance (40.8%) [12].

Thereby NS is a chronic condition with the treatment of SRNS being a difficult task [9].

The most important predictor of long-term outcome is complete or partial remission of proteinuria with patients with persistent proteinuria at risk for progressive renal failure [13]. The response of Proteinuria to therapy is an essential determinant of Renal survival [14] as determined by the Data from PodoNet Registry on patients with SRNS which shows that 10-year survival was highest (94%) in complete remission, 72% with partial remission and 43% with non-response [15]. There are no studies on clinical profile and management options in SRNS in our region. Hence, need of this study is required.

6.2 REVIEW OF LITERATURE

Use of Tacrolimus in a RCT trial conducted by Choudhary et al in a tertiary-care hospital with 41 consecutive patients with idiopathic SRNS, estimated glomerular filtration rate greater than 60 mL/min/1.73 m2, and histological characteristics showing minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis were randomly assigned to treatment with tacrolimus (n = 21) or CsA (n = 20). Tacrolimus (0.1 to 0.2 mg/kg/d) or CsA (5 to 6 mg/kg/d) was given for 1 year, cotreatment with alternate-day prednisolone and enalapril.

Tacrolimus or csa in combination with low-dose steroids show similar efficacy in inducing remission in patients with SRNS. Therapy with tacrolimus is a promising alternative to csa in view of the lower risk of relapses and lack of cosmetic side effects [9]

Another study by Becknell B et al. suggested tacrolimus to have better results in steroid resistant cases [11].

Loeffler et al. [16] reported the use of tacrolimus in seven children with SRNS; six children achieved CR and one went into PR after a mean duration of 2 months of therapy. Five of the seven children were off steroids on follow-up, although the steroid-free duration was quite short.

Children with steroid-resistant nephrotic syndrome (SRNS) are at risk of developing renal failure. A study by Butani L et al showed results of a single-center retrospective observational study of the remission rate in pediatric patients with SNRS receiving tacrolimus. Serial renal biopsies from children on tacrolimus therapy were evaluated for tubulointerstitial fibrosis and transforming growth factor-beta immunostaining. Of the 16 children with SRNS, 15 went into complete remission after a median of 120 days of therapy. Nine children were able to stop steroids, while the others were on tapering doses. Forty-seven percent had relapses, most of which were steroid-responsive. Serial renal biopsies were obtained from seven children after a median treatment duration of 24 months; two of these children had increased tubulointerstitial fibrosis and four showed

increased transforming growth factor-beta tissue staining. Children with worsening histological findings were younger. There was no significant association between tacrolimus exposure and biopsy changes, although the average trough level was higher in those children with worsening histological findings. In conclusion, tacrolimus may be a safe and effective alternative agent for inducing remission in children with SRNS [17].

A retrospective chart review was performed by Straatmann C et al on patients diagnosed with idiopathic NS and subsequent LSR during the 8-year study period from 2002 up to and including 2009, with a minimum of 2 years of follow-up. Primary outcome measures were proteinuria and renal function. A total of 29 patients were classified as having LSRNS. The majority of patients received treatment with calcineurin inhibitors and/or mycophenolate mofetil. Seven patients received three or more non-steroid immunosuppressant medications. Sustained complete or partial remission was achieved in 69 % of patients. Three developed end stage renal disease, and all others maintained normal renal function. There were 13 episodes of serious adverse events, none of which were fatal or irreversible. Thereby most patients with LSRNS responded to immunosuppressive therapy by reduction or resolution of proteinuria and preservation of renal function. The results suggest that immunosuppressive treatment is a viable option in NS patients who develop LSR [18].

Another study at AIIMS delhi by following six months of therapy with tacrolimus, patients with complete or partial remission were randomly assigned such that 29 received MMF while 31 received tacrolimus along with tapering prednisolone on alternate days for 12 months. The proportion of patients with a favorable outcome (sustained remission, infrequent relapses) at one year was significantly lower (44.8%) in the MMF group than in the tacrolimus group (90.3%). The incidence of relapses was significantly higher for patients treated with MMF than tacrolimus (mean difference: 1.05 relapses per person-year). While there

was no difference in the proportion of patients with sustained remission, the risk of recurrence of steroid resistance was significantly higher for patients receiving MMF compared to tacrolimus (mean difference: 20.7%). Compared to tacrolimus, patients receiving MMF had a significantly (71%) lower likelihood of a favorable outcome and significantly increased risk of treatment failure (frequent relapses, steroid resistance). Thus, replacing tacrolimus with MMF after six months of tacrolimus therapy for steroid-resistant nephrotic syndrome in children is associated with significant risk of frequent relapses or recurrence of resistance concluding tacrolimus to be superior to mycophenolate mofetil in sustaining remission in children with idiopathic steroid resistant nephrotic syndrome [19].

A retrospective chart reviews of 18 children, received prednisolone at the start of tacrolimus. 72.2% children achieved complete response (CR), medicine was well tolerated and treatment was effective [20].

In a prospective non-randomized, non-controlled study by chen, HX., Cheng, Q., Li, F. *Et al.*, Chinese children with SRNS who failed the previous full-dose prednisone treatment were given tacrolimus (0.1 mg/kg/day) and low-dose prednisone (0.25–0.50 mg/kg/day) and compared the overall remission rate (ORR) and adverse events in the follow-up period with this therapeutic regimen. A total of 76 children were enrolled into the study with an average follow-up period of 18 ± 6 months (maximum 36 months). ORR achieved by the first, third, and sixth months was 94.7%, 94.7%, and 96.0%, respectively. All patients who attained an initial tacrolimus trough concentration ($fk506c_0$) > 6 ng/ml (60.3%) achieved remission. The relative risk of relapse at $fk506c_0 < 3$ ng/ml compared to 3–6 ng/ml, 6–9 ng/ml, and 9–12 ng/ml was 2.3, 3.2, and 16.9, respectively. During the follow-up period, adverse effects that had been previously reported were rare [21].

A controlled trial conducted by Eduardo H. Garin, MD et al [22] a on the efficacy of cyclosporine in eight patients with steroid-resistant nephrotic syndrome (four with idiopathic minimal lesion nephrotic

syndrome and four with focal segmental glomerulosclerosis). Patients were randomly allocated to a cyclosporine (5 mg/kg/d) or a control group. After eight weeks of therapy and one month without cyclosporine therapy, patients in the control group were given cyclosporine for eight weeks and those in the cyclosporine group became controls. Before the initiation of treatment, there was no difference between the groups with regard to proteinuria and serum albumin levels. Proteinuria remained unchanged in the cyclosporine group, while there was a significant increase in proteinuria in the control group. There were no significant changes in serum albumin levels in either group during the trial. This study does not support the use of cyclosporine at the dose of 5 mg/kg/d in patients with steroid-resistant minimal lesion nephrotic syndrome or focal segmental glomerulosclerosis.

Status of patients are defined according to the following categories:

Remission- Urine albumin nil or trace for 3 consecutive early morning specimens,

Relapse- Urine albumin 3+ or 4+ for 3 consecutive early morning specimens, Up/Uc>2, or 24-hr protein >1000 mg/m2 /day, in a patient previously in partial or complete remission

Sustained remission- No relapse for 1 year

Frequent relapsers- Two or more relapses in initial six months or more than three relapses in any twelve months.

Infrequent Relapsers -Patients who have three or less relapses a year

Steroid resistance- Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks.

6.3 AIMS AND OBJECTIVES OF THE STUDY

TO STUDY:

1. CLINICAL PROFILE OF CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME (SRNS)
2. TREATMENT PRACTICES AND OUTCOMES IN THESE SRNS CHILDREN

7. MATERIAL AND METHODS

7.1 Design – Observational study.

SETTING – Nephrology clinic of a tertiary care hospital, DMCH Ludhiana

SOURCE OF DATA

Source of data will be patients between 3 months to 18 years of age who are

1) Newly diagnosed SRNS cases

2) Follow up of those patients who are already known case of SRNS and are on immunosuppressants for at least 6 months.

INCLUSION CRITERIA

- All newly diagnosed SRNS patients (Nephrotic syndrome children >=3+ dipstick, proteinuria >40mg/m2 /hr (>1000mg/m2/day), Up/Ucr >=2mg/mg, Hypoalbuminaemia (<3gm/dl) and edema) who have recieved 4 weeks of full dose steroids (2mg/kg/day) and there is absence of complete remission.
- All SRNS patients who are already on Immunosuppressants with follow up of at least 6 months.

EXCLUSION CRITERIA

- Patients of congenital Nephrotic syndrome (age at onset <3 months)
- Patients with nephrotic syndrome due to secondary causes.
- Steroid Sensitive Nephrotic Syndrome
- If attendants refused to give consent for participation in the study.

CONSENT

Written consent will be obtained from the attendants of the children. Patients will be assessed appropriately and data will be collected on specified patient proforma including information such as age, sex, Steroid Resistant Early/Late, Age of onset, weight, height, BMI, side effects.

Classification of Response-

Responder = Patient who are in Complete remission/ Partial remission at 6 months of treatment.

Non-Responder = Patient showing no response to treatment.

Complete remission defined as the Urine albumin nil or trace for 3 consecutive early morning specimens, Up/Uc <0.2, or 24-hr protein <100mg/m^2/day;

Partial remission, as 1+/2+(dipstick), Up /Uc 0.2-2, or 24-hr protein 100-1000mg/m^2/day; serum albumin >=3gm/dl; and absence of edema;

Nonresponse as 3+/4+(dipstick), Up/Uc >2 or 24-hr urine protein >1000mg/m^2/day; Albumin < 3 g/dL or edema

Treatment failure, defined in patients showing no response despite 6 months of treatment, persistent nephrotoxicity, or death.

7.2 METHOD OF COLLECTION OF DATA

It will be an observational hospital-based study of patients from August, 2021 to May, 2022 of SRNS who will be newly diagnosed along with patients who are already known case of SRNS and are on immunosuppression with follow up of at least 6 months.

Outcome

Primary outcome -The primary end point is the proportion of patients achieving complete or partial remission at the end of 6 months of therapy.

Secondary outcome include frequency of relapses, renal dysfunction and side effects from immunosuppressive medications.

Statistical analysis

Analysis will be done by SPSS 21.0 (Statistical Product and Service Solutions Chicago 21.0 version)

Continuous data will be presented as mean, 95% confidence interval (CI), and range unless other- wise stated.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY

Yes; Investigations pertaining to diagnosis of SRNS and follow up of these patients.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF?

Yes, attached herewith.

8. LIST OF REFERENCES

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PROFORMA

SRNS FILE RECORD

S.No.

NAME

AGE

SEX

RURAL/URBAN

MRD NO:

STEROID RESISTANT: EARLY / LATE

AGE OF ONSET

STEROID TOXICITY FEATURES: CUSHINGOID

FEATURES/CATARACT

RENAL BIOPSY (IF DONE)

ATYPICAL FEATURES: HAEMATURIA/ HYPERTENSION/ RENAL

FAILURE

GENETIC TESTING (IF DONE)

FAMILY HISTORY / ANY SIBLING AFFECTED

WEIGHT/HEIGHT/BMI

BASELINE INVESTIGATIONS: CBC

RFT

VIRAL MARKERS

SERUM ALBUMIN

SERUM GLUCOSE

Signature of Candidate

Signature of Supervisor

THYROID PROFILE

LIPID PROFILE

VITAMIN D LEVEL

CALCIUM

PHOSPHATE

ALKALINE PHOSPHATASE

URINE ROUTINE

SPOT URINARY PROTEIN

CREATININE RATIO

24 HOUR URINARY PROTEIN

ULTRASOUND ABDOMEN

CHEST XRAY

IMMUNOSUPPRESSIVE THERAPY

ADDITIONAL DRUGS CONTINUED:

Signature of Candidate

Signature of Supervisor

A) NEWLY DIAGNOSED CASES

1) TACROLIMUS

INITIAL DOSAGE:

MONITORING

MONTH	URINE ALBUMIN	URINE PROTEIN CREATININE RATIO	24 HR URINE PROTEIN	SERUM ALBUMIN	SERUM CREATININE	ELECT ROLYTES	TACRO LIMUS LEVELS	EDEMA	ANY OTHER SIDE EFFECT	DOSAGE LEVELS
1										
3										
6										

RESULTS:

STATUS OF PATIENTS AT 3 MONTHS: CR/PR/NR

STATUS OF PATIENTS AT 6 MONTHS: CR/PR/NR

RELAPSE: YES/ NO

Signature of Candidate

Signature of Supervisor

2. CYCLOSPORINE

INITIAL DOSAGE:

MONITORING

MONTH	URINE ALBUMIN	URINE PROTEIN CREATININE RATIO	24 HR URINE PROTEIN	SERUM ALBUMIN	SERUM CREATININE	ELECTROL YTES	EDEMA	ANY OTHER SIDE EFFECT	DOSAGE LEVELS
1									
3									
6									

RESULTS:

STATUS OF PATIENTS AT 3 MONTHS: CR/PR/NR

STATUS OF PATIENTS AT 6 MONTHS: CR/PR/NR

RELAPSE: YES/ NO

Signature of Candidate

Signature of Supervisor

B) FOLLOW UP CASES:

CYCLOSPORINE/ TACROLIMUS

DOSAGE:

MONTH	URINE ALBUMIN	URINE PROTEIN CREATININE RATIO	24 HR URINARY PROTEIN	SERUM ALBUMIN	SERUM CREATININE	ELECTROL YTES	EDEMA	ANY OTHER SIDE EFFECT	DOSAGE LEVELS
1									
3									
6									

STATUS OF PATIENTS AT 3 MONTHS: CR/PR/NR

STATUS OF PATIENTS AT 6 MONTHS: CR/PR/NR

DURATION FOR WHICH IMMUNOSUPPRESSANT GIVEN:

CHANGE OF THERAPY: YES / NO

INDICATION OF CHANGE OF THERAPY:

RELAPSE: YES/ NO

NUMBER OF RELAPSES:

Signature of Candidate

Signature of Supervisor

PATIENT'S PARENT / GUARDIAN CONSENT FORM

Date: ____/____/____

I .....F/o, M/o ..... R/o
.....
. am willing to let my child participate in the study entitled Bed **"CLINICAL PROFILE, TREATMENT PRACTICES AND OUTCOMES IN CHILDREN WITH STEROID RESISTANT NEPHROTIC SYNDROME"**. The procedure with its complications have been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason. This will not affect my treatment and investigation of my child.

_____	_____
Signature of the Witness	Signature/Thumb Impression of guardian
Name:	Name:

मरीज के माता/पिता का अनुमति फार्म

तिथि___/___/___

मैं_____ पिता/माता/_____
वासी_____,
अपने बच्चे के इस शोधकार्य में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य मेंभागलेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता / करती हूँ कि स्वीकृत देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और नही दबाव डाला गया है । मुझे इस शोध कार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है कि यह विज्ञान और मानवता के लाभ के लिए है । मुझे इस शोध कार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामूलीहै।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे बच्चे के इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____
गवाह के हस्ताक्षर मरीज के माता/पिता के हस्ताक्षर

तिथि_____

पता_____

_____ _____
नरीक्षक के हस्ताक्षर प्रत्याक्षी के हस्ताक्षर

ਮਰੀਜ ਦੇ ਮਾਤਾ/ਪਿਤਾ ਦਾ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ __/___/____

ਮੈਂ _____ ਪਿਤਾ/ਮਾਤਾ _____,

ਵਾਸੀ _____

ਆਪਣੇ ਬੱਚੇ ਦੇ ਇਸ ਅਧਿਐਨ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਤੇ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈਂ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈਂ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ/ਚਾਹੁੰਦੀ ਹਾਂ ਕਿ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂੰ ਕਿਸੇ ਵੀ ਤਰ੍ਹਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀਂ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਵਿੱਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆਂ ਹੈ ਅਤੇ ਮੈਨੂੰ ਇਹ ਯਕੀਨ ਹੈ ਕਿ ਇਹ ਖਤਰਾ ਬਹੁਤਾ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂੰ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ-ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈਂ ਇਸ ਖੋਜ ਕੰਮ ਵਿੱਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇਂ ਵਾਪਸ ਲੈ ਸਕਦਾ/ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਬੱਚੇ ਦੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀਂ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ _____ ਮਿਤੀ _____

ਪਤਾ _____ ਪਤਾ _____

_____ _____

ਨਰੀਖਕ ਦੇ ਹਸਤਾਖਰ ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ